STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 138948

TO: Shailendra Kumar Location: 5c03 / 5c18 Wednesday, December 01, 2004 Art Unit: 1621 Phone: 272-0640 Serial Number: 10 / 691465	From: Jan Delaval Location: Biotech-Chem Library Rem 1A51 Phone: 272-2504 jan.delaval@uspto.gov

Search Notes

Jan please

Scientific and Technical Information Center 138948

Requester's Full Name: S. Kumar Examiner #: 69594 Date: 11/30/04
Art Unit: 1621 Phone Number 30 2-0640 Serial Number: 10/691,465
Mail Box and Bldg/Room Location: REM 5C03 5C18 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

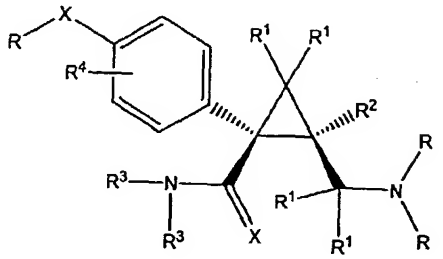
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of invention: Stereoisomers of β-hydroxy milnacipran and method ...

Inventors (please provide full names): Roman V. Rariy et al.

Earliest Priority Filing Date: 10/25/2002

1. An isolated compound represented by **A**:



A

wherein

X represents independently for each occurrence O, S, or NR;

R represents independently for each occurrence H, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, formyl, acyl, silyl, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$;

R^1 represents independently for each occurrence H, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylakylamino, sulfhydryl, alkylthio, arylthio, arylakylthio, nitro, azido, alkylseleno, formyl, acyl, carboxyl, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$;

R^2 represents independently for each occurrence H, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, or $-(CH_2)_m-R_{80}$;

R^3 represents independently for each occurrence H, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, or $-(CH_2)_m-R_{80}$;

R^4 is absent or present between one and four times inclusive;

R^4, if present, represents independently for each occurrence H, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylakylamino, sulfhydryl, alkylthio, arylthio, arylakylthio, nitro, azido, alkylseleno, formyl, acyl, carboxyl, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence an aryl, cycloalkyl, cycloalkenyl,

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 08:12:16 ON 01 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   29 NOV 2004  HIGHEST RN 790629-40-2
DICTIONARY FILE UPDATES:  29 NOV 2004  HIGHEST RN 790629-40-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sta que l9
L7                  STR
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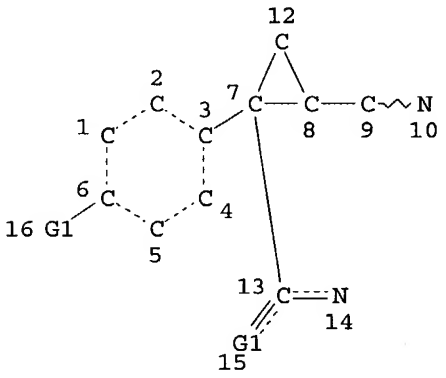


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VAR G1=O/S/N
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   8   3
NUMBER OF NODES IS  15

STEREO ATTRIBUTES: NONE
L9            25 SEA FILE=REGISTRY SSS FUL L7

100.0% PROCESSED     30 ITERATIONS                    25 ANSWERS
SEARCH TIME: 00.00.01


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               SET COST OFF
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L2           497 S COLLEGIUM?/PA,CS
                 E RARIY R/AU
L3            16 S E4-E6
                 E HEFFERNAN M/AU
L4            67 S E3-E6,E11-E16,E19
                 E BUCHWALD S/AU
L5           327 S E3,E4,E6-E9
                 E SWAGER T/AU
L6           340 S E3-E9

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L7               STR
L8             3 S L7
L9            25 S L7 FUL
                 SAV L9 KUMAR691/A
                 E CS1713/CN
                 E CS 1713/CN
L10            3 S E3,E4,E10
L11           22 S L9 NOT L10

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L12            0 S L10
L13            0 S L11

     FILE 'HCAPLUS' ENTERED AT 08:06:56 ON 01 DEC 2004
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L16            7 S L11
L17            7 S L14-L16
L18            3 S L17 AND L1-L6
L19            2 S F2782 OR CS1628 OR CS1649 OR CS1665 OR CS1710 OR CS1658
L20            3 S F 2782 OR CS()(1628 OR 1649 OR 1665 OR 1710 OR 1658)
L21            7 S L17-L20

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L22            0 S L10
L23            4 S L11
L24            6 S L15 OR L19 OR L20
L25            9 S L23,L24

     FILE 'REGISTRY' ENTERED AT 08:12:16 ON 01 DEC 2004

=> d ide can tot l10

L10  ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   688320-04-9  REGISTRY
CN   Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-,
     monohydrochloride, (1R,2S)-rel- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   CS 1814
FS   STEREOSEARCH
MF   C15 H22 N2 O2 . Cl H
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER
DT.CA  CAplus document type:  Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); USES
       (Uses)

Relative stereochemistry.
Currently available stereo shown.
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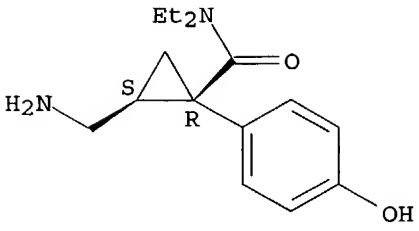


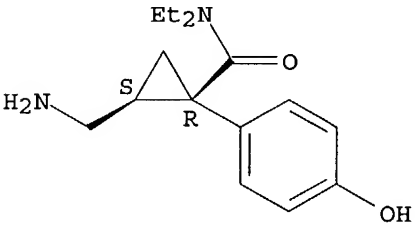
● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

L10 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 688320-03-8 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, monohydrochloride, (1R,2S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **CS 1714**
FS STEREOSEARCH
MF C15 H22 N2 O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (688738-12-7)

Absolute stereochemistry.



● HCl

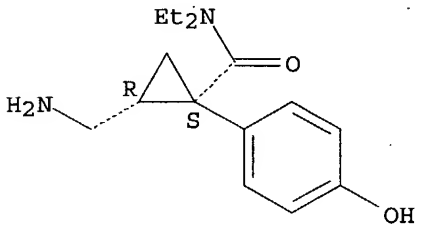
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

L10 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 688320-02-7 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, monohydrochloride, (1S,2R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **CS 1713**
FS STEREOSEARCH

MF C15 H22 N2 O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (688738-11-6)

Absolute stereochemistry.



● HCl

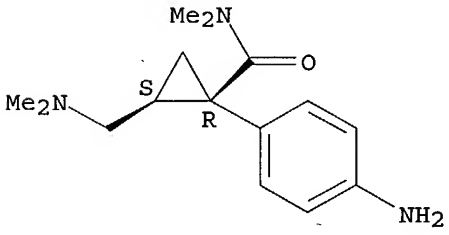
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

=> d ide can tot l11

L11 ANSWER 1 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 790163-07-4 REGISTRY
CN INDEX NAME NOT YET ASSIGNED
FS STEREOSEARCH
MF C15 H23 N3 O
CI COM
SR CA

Relative stereochemistry.

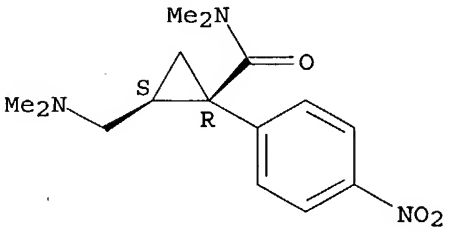


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L11 ANSWER 2 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 789445-10-9 REGISTRY
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-N,N-dimethyl-1-(4-nitrophenyl)-, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H21 N3 O3
CI COM

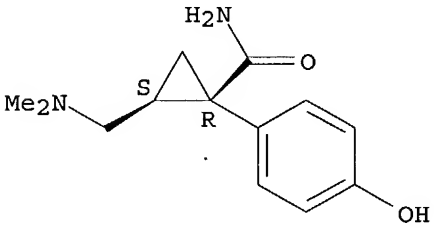
SR CA

Relative stereochemistry.



L11 ANSWER 3 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 770664-37-4 REGISTRY
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-1-(4-hydroxyphenyl)-, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C13 H18 N2 O2
CI COM
SR CA

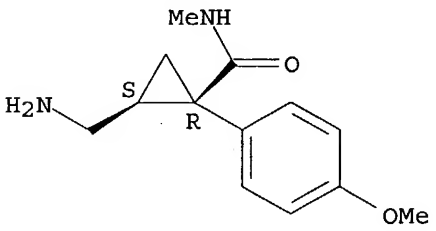
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L11 ANSWER 4 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 746573-65-9 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-N-methyl-, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C13 H18 N2 O2
CI COM
SR CA

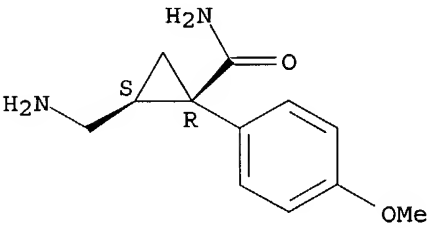
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L11 ANSWER 5 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 742015-78-7 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C12 H16 N2 O2
CI COM
SR CA

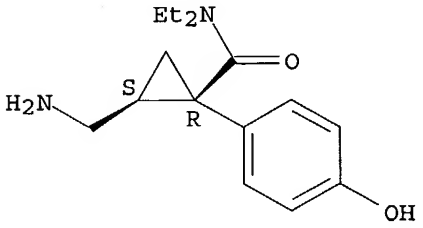
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L11 ANSWER 6 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 688738-12-7 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CS 1710
FS STEREOSEARCH
MF C15 H22 N2 O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

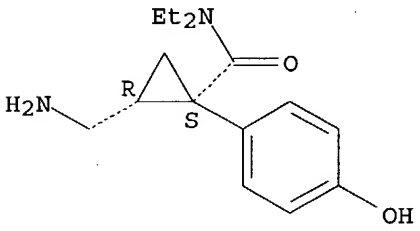
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

L11 ANSWER 7 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 688738-11-6 REGISTRY

CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1S,2R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CS 1665
FS STEREOSEARCH
MF C15 H22 N2 O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



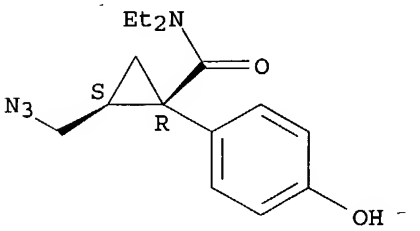
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

L11 ANSWER 8 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 688320-09-4 REGISTRY
CN Cyclopropanecarboxamide, 2-(azidomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CS 1658
FS STEREOSEARCH
MF C15 H20 N4 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: RACT (Reactant or reagent)

Absolute stereochemistry.



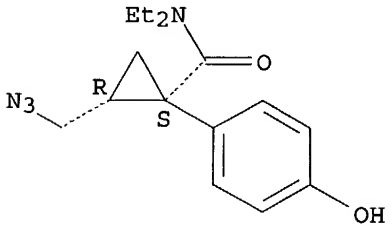
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

L11 ANSWER 9 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN

RN 688320-08-3 REGISTRY
CN Cyclopropanecarboxamide, 2-(azidomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1S,2R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CS 1649
FS STEREOSEARCH
MF C15 H20 N4 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

L11 ANSWER 10 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 688320-07-2 REGISTRY
CN Cyclopropanecarboxamide, 2-(azidomethyl)-N,N-diethyl-1-(4-methoxyphenyl)-, (1S,2R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CS 1628
FS STEREOSEARCH
MF C16 H22 N4 O2
SR CA
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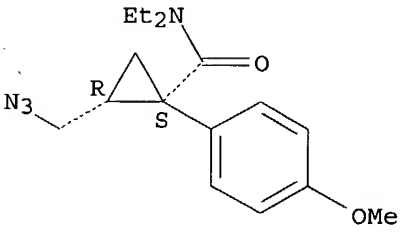
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



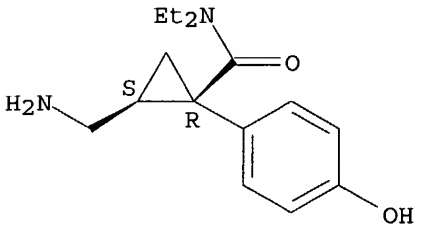
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:400095

L11 ANSWER 11 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 686766-17-6 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)-rel- (9CI) (CA INDEX NAME)

OTHER NAMES:
CN F 2782
CN parahydroxy-milnacipran
FS STEREOSEARCH
MF C15 H22 N2 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:185117

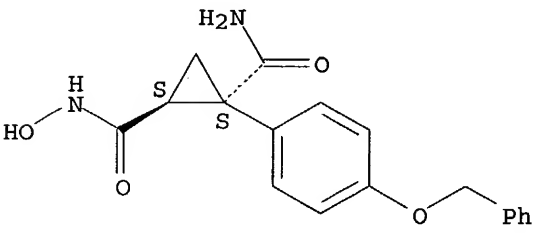
REFERENCE 2: 141:162416

REFERENCE 3: 140:400095

REFERENCE 4: 140:395521

L11 ANSWER 12 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 556109-05-8 REGISTRY
CN 1,2-Cyclopropanedicarboxamide, N2-hydroxy-1-[4-(phenylmethoxy)phenyl]-, (1S,2S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C18 H18 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



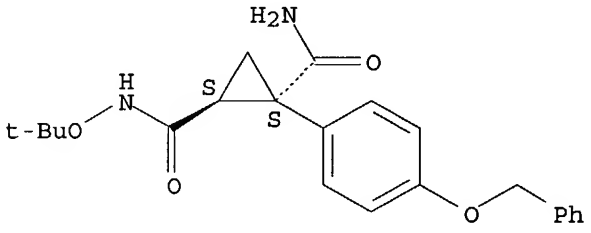
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:85038

L11 ANSWER 13 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 556105-54-5 REGISTRY
CN 1,2-Cyclopropanedicarboxamide, N2-(1,1-dimethylethoxy)-1-[4-(phenylmethoxy)phenyl]-, (1S,2S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



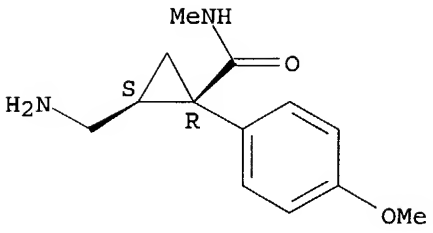
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:85038

L11 ANSWER 14 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 136091-14-0 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-N-methyl-, monohydrochloride, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C13 H18 N2 O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study)
CRN (746573-65-9)

Relative stereochemistry.



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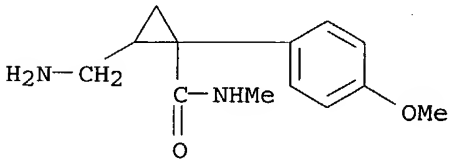
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 115:239722

L11 ANSWER 15 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 136090-95-4 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-N-methyl-
(9CI) (CA INDEX NAME)
MF C13 H18 N2 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study)

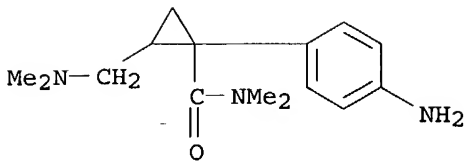


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 115:239722

L11 ANSWER 16 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 136090-93-2 REGISTRY
CN Cyclopropanecarboxamide, 1-(4-aminophenyl)-2-[(dimethylamino)methyl]-N,N-
dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C15 H23 N3 O
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study)

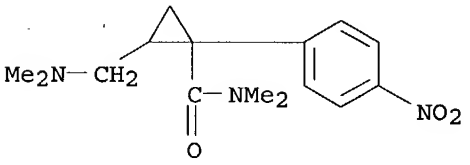


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 115:239722

L11 ANSWER 17 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 136090-92-1 REGISTRY
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-N,N-dimethyl-1-(4-nitrophenyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C15 H21 N3 O3
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study)

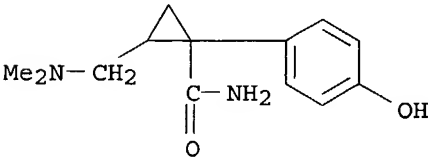


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 115:239722

L11 ANSWER 18 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 136090-91-0 REGISTRY
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-1-(4-hydroxyphenyl)-(9CI) (CA INDEX NAME)
MF C13 H18 N2 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study)



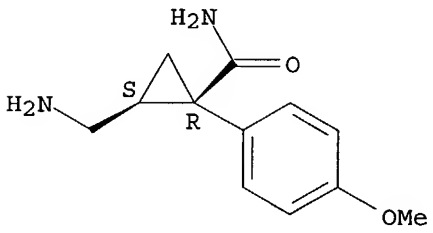
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 115:239722

L11 ANSWER 19 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 86181-21-7 REGISTRY
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C12 H16 N2 O2 . Cl H
LC STN Files: CA, CAPLUS, RTECS*, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation)
CRN (742015-78-7)

Relative stereochemistry.



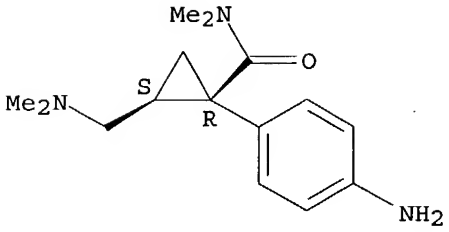
● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 99:22001

L11 ANSWER 20 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 86181-19-3 REGISTRY
CN Cyclopropanecarboxamide, 1-(4-aminophenyl)-2-[(dimethylamino)methyl]-N,N-dimethyl-, monohydrochloride, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H23 N3 O . Cl H
LC STN Files: CA, CAPLUS, RTECS*, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation)
CRN (790163-07-4)

Relative stereochemistry.



● HCl

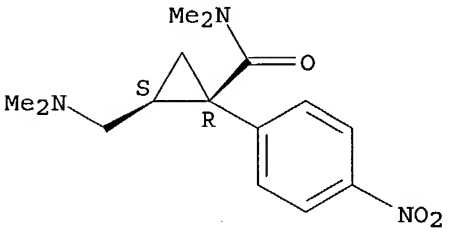
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 115:239722

REFERENCE 2: 99:22001

L11 ANSWER 21 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 86181-18-2 REGISTRY
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-N,N-dimethyl-1-(4-nitrophenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H21 N3 O3 . Cl H
LC STN Files: CA, CAPLUS, RTECS*, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation)
CRN (789445-10-9)

Relative stereochemistry.



● HCl

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

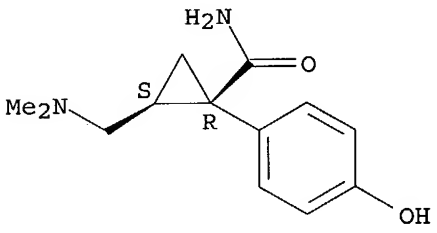
REFERENCE 1: 115:239722

REFERENCE 2: 99:22001

L11 ANSWER 22 OF 22 REGISTRY COPYRIGHT 2004 ACS on STN
RN 86181-17-1 REGISTRY
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-1-(4-hydroxyphenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

FS STEREOSEARCH
MF C13 H18 N2 O2 . Cl H
LC STN Files: CA, CAPLUS, RTECS*, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation)
CRN (770664-37-4)

Relative stereochemistry.



● HCl

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 115:239722

REFERENCE 2: 99:22001

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:12:38 ON 01 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 1 Dec 2004 VOL 141 ISS 23
FILE LAST UPDATED: 29 Nov 2004 (20041129/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> => d l21 all hitstr tot

L21 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:681408 HCAPLUS
DN 141:185117
ED Entered STN: 20 Aug 2004
TI Dextrogyral enantiomer of milnacipran as double inhibitors of serotonin

and norepinephrine reuptake
IN Deregnaucourt, Jean; Grosse, Richard
PA Fr.
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-4015
ICS A61K031-195; A61K031-165
NCL 514424000; 514567000; 514617000
CC 1-11 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004162334	A1	20040819	US 2003-453574	20030603
FR 2851163	A1	20040820	FR 2003-1849	20030214
WO 2004075886	A1	20040910	WO 2004-FR347	20040216

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI FR 2003-1849 A 20030214
US 2003-453574 A 20030603

CLASS

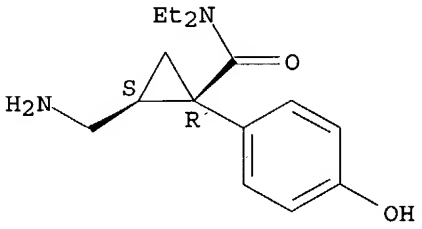
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004162334	ICM	A61K031-4015
	ICS	A61K031-195; A61K031-165
	NCL	514424000; 514567000; 514617000
US 2004162334	ECLA	A61K031/135+M; A61K031/165; A61K031/165+M; A61K031/195+M; A61K031/4015+M
FR 2851163	ECLA	A61K031/135+M; A61K031/165; A61K031/165+M; A61K031/195+M; A61K031/4015+M

AB The present invention concerns the use of a mixture of enantiomers enriched in the dextrogyral enantiomer of milnacipran and/or of at least one of its metabolites, as well as their pharmaceutically-acceptable salts, for the preparation of a drug intended to prevent or to treat disorders that can be managed by double inhibition of serotonin (5-HT) and norepinephrine (NE) reuptake, while limiting the risks of cardiovascular disturbances and/or organ and/or tissue toxicity.

ST dextrogyral enantiomer milnacipran serotonin reuptake inhibitor
IT Cardiovascular system, disease
Psychotropics
(dextrogyral enantiomer of milnacipran as double inhibitors of serotonin and norepinephrine reuptake)
IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dextrogyral enantiomer of milnacipran as double inhibitors of serotonin and norepinephrine reuptake)
IT 92623-85-3, Milnacipran 96847-54-0 96847-55-1 105310-34-7, F 2941 105310-35-8, F 2800 **686766-17-6, F2782**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dextrogyral enantiomer of milnacipran as double inhibitors of serotonin and norepinephrine reuptake)

IT 105310-28-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dextrogyral enantiomer of milnacipran as double inhibitors of serotonin and norepinephrine reuptake)
IT **686766-17-6, F2782**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dextrogyral enantiomer of milnacipran as double inhibitors of serotonin and norepinephrine reuptake)
RN 686766-17-6 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L21 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:648413 HCAPLUS
DN 141:162416
ED Entered STN: 12 Aug 2004
TI Multiparticulate compositions of milnacipran for oral administration
IN Hirsh, Jane; Fleming, Alison B.; **Rariy, Roman V.**
PA **Collegium Pharmaceutical, Inc., USA**
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K047-48
CC 63-6 (Pharmaceuticals)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004067039	A1	20040812	WO 2004-US2346	20040128
	W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI				
	US 2004228830	A1	20041118	US 2004-766124	20040128
PRAI	US 2003-443237P	P	20030128		
	US 2003-443618P	P	20030129		
	US 2003-458993P	P	20030328		
	US 2003-468470P	P	20030506		
	US 2003-490060P	P	20030724		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004067039	ICM	A61K047-48

AB A multiparticulate composition for oral administration of milnacipran or its active metabolite (p-hydroxymilnacipran, **F2782**) is developed.
The formulation is made by complexing milnacipran with an ion-exchange

resin in the form of small particles, typically less than 150 μ. Multiparticulate formulations may be any one or more of the following types of particles formulated into a final dosage form: (i) immediate-release particles, prepared by coating drug-containing particles with the polymer that is insol. in the neutral medium of saliva, but dissolves in the acid environment of the stomach; (ii) enteric-coated particles, prepared by coating drug-containing particles with the polymer that is insol. in the acidic environment of the stomach but dissolves in the neutral environment of the small intestines; (iii) extended-release particles, prepared by coating drug-containing particles with a polymer that forms water insol. but water permeable membrane; (iv) enteric coated-extended release particles, prepared by coating extended release drug particles with a second, enteric coating; and (v) delayed-release particles, prepared by coating drug-containing particles with a polymer that is insol. in the acidic environment of the stomach and the environment of the upper small intestines, but dissolves in the lower small intestines or upper large intestines. The various drug-containing particles described above can be further formulated into a number of different final dosage forms including, but not limited. to, a liquid, liquid suspension, gel, capsule, soft gelatin capsule, tablet, chewable tablet, crushable tablet, rapidly dissolving tablet, or unit of use sachet or capsule for reconstitution. The final dosage forms further comprises one or more addnl. active ingredients, e.g., analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimuscarinics, anxiolytics, sedatives, etc. For example, 3 L of deionized water was added to 700.00 g of pre-washed Amberlite IRP-69 resin particles and kept under stirring. Milnacipran-HCl 400.00 g was added to the resin slurry while mixing. and the supernatant from the resulting mixture was decanted off allowing the resin to settle for 30 min. The drug-loaded resin particles were then washed and dried until the loss on drying was less than 10%. The uncoated milnacipran-resin complex did not have any extended release properties. However, the coating of milnacipran-resin complex with Eudragit RS 30D was capable of controlling the release of drug.

ST milnacipran hydroxymilnacipran ion exchanger particle oral

IT Drug delivery systems
(capsules, soft; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Drug delivery systems
(capsules; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Drug delivery systems
(enteric-coated, particles; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Drug delivery systems
(gels; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Drug delivery systems
(liqs.; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Ion exchangers
Particle size
(multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

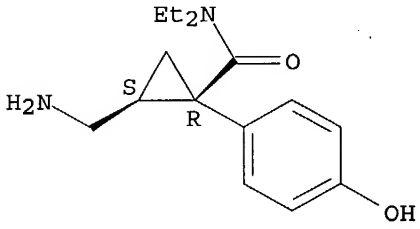
IT Drug delivery systems
(particles; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Drug delivery systems
(sachets; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Drug delivery systems
(suspensions, oral; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)

IT Drug delivery systems
(sustained-release, particles; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)
IT Drug delivery systems
(tablets, chewable; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)
IT Drug delivery systems
(tablets; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)
IT 25212-88-8, Eudragit L30 D55 33434-24-1, Eudragit RS 30D
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coating; multiparticulate compns. for oral administration of milnacipran containing ion exchanger)
IT 55464-99-8, Amberlite IRP-69 92623-85-3, Milnacipran 101152-94-7, Milnacipran hydrochloride **686766-17-6, F 2782**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multiparticulate compns. for oral administration of milnacipran containing ion exchanger)
IT **686766-17-6, F 2782**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multiparticulate compns. for oral administration of milnacipran containing ion exchanger)
RN 686766-17-6 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L21 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:392439 HCAPLUS
DN 140:400095
ED Entered STN: 14 May 2004
TI Stereoisomers of p-hydroxy-milnacipran, and therapeutic use
IN **Rariy, Roman V.; Heffernan, Michael; Buchwald, Stephen L.; Swager, Timothy M.**
PA **Collegium Pharmaceutical, Inc., USA**
SO PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-11 (Pharmacology)
Section cross-reference(s): 25, 63
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004039320	A2	20040513	WO 2003-US33681	20031022 <--
WO 2004039320	A3	20040624		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,

PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG,
KZ, MD, RU, TJ
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

US 2004142904 A1 20040722 US 2003-691465 20031022 <--
PRAI US 2002-421640P P 20021025 <--
US 2002-423062P P 20021101 <--
US 2003-445142P P 20030205 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004039320	ICM	A61K

OS MARPAT 140:400095

AB The invention relates generally to the enantiomers of p-hydroxymilnacipran or congeners thereof. Biol. assays revealed that racemic p-hydroxymilnacipran is approx. equipotent in inhibiting serotonin and norepinephrine uptake (IC50 = 28.6 nM for norepinephrine, IC50 = 21.7 nM for serotonin). Interestingly, (+)-p-hydroxymilnacipran is a more potent inhibitor of norepinephrine uptake than serotonin uptake (IC50 = 10.3 nM for norepinephrine, IC50 = 22 nM for serotonin). In contrast, (-)-p-hydroxymilnacipran is a more potent inhibitor of serotonin uptake compared to norepinephrine uptake (IC50 = 88.5 nM for norepinephrine, IC50 = 40.3 nM for serotonin). The invention also relates to salts and prodrug forms of the above compds. In certain embodiments, the compds. of the invention and a pharmaceutically acceptable excipient are combined to prepare a formulation for administration to a patient. Finally,the invention relates to methods of treating mammals suffering from various afflictions, e.g., depression, chronic pain, or fibromyalgia, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of the invention. Compound preparation is included.

ST hydroxymilnacipran stereoisomer prepn therapeutic depression; chronic pain fibromyalgia therapeutic hydroxymilnacipran stereoisomer; serotonin norepinephrine reuptake hydroxymilnacipran stereoisomer

IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A2A; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Bradykinin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(B1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Bradykinin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(B2; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Dopamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Dopamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D1A; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Dopamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D2(long); p-hydroxymilnacipran stereoisomers, therapeutic use, and use

with other agents)
IT Dopamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D3; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Dopamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D4, D4.2; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GABA transporter; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT GABA receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GABAA, agonist site; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT GABA receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GABAA, benzodiazepine, central; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT GABA receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GABAB, benzodiazepine, central; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Histamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Histamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H2; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Histamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H3; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Imidazoline receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(I2, central; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Calcium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(L-type, benzothizepine; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Calcium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(L-type, dihydropyridine; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Muscarinic receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(M1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Muscarinic receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(M2; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Muscarinic receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(M3; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Calcium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(N-type; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA-binding, glycine; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA-binding, phencyclidine; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA-binding; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Purinoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(P2X; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Purinoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(P2Y; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Neuropeptide Y receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Y1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Neuropeptide Y receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Y2; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Mental disorder
(affective; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Nervous system agents
(antinarcoleptics; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Mental disorder
(attention deficit hyperactivity disorder; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Glucocorticoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(benzodiazepine, central; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(buccal; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Fatigue, biological
(chronic fatigue syndrome; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Bladder, disease
(cystitis, interstitial; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Mental disorder
(depression; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine transporter; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Head
(face, atypical face pain; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Muscle, disease

(fibromyalgia; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Disease, animal
(functional somatic disorders; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Dyspepsia
(functional; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drugs
(gastrointestinal; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Anxiety
(generalized; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(injections, i.m.; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(injections, i.v.; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(injections, s.c.; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Intestine, disease
(irritable bowel syndrome; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(kainate-binding; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Leukotriene receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(leukotriene D4; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Headache
(migraine; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(nasal; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Mental disorder
(neurotic depression; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Thorax
(noncardiac chest pain; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(norepinephrine transporter; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Nutrition, animal
(nutritional agents; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Mental disorder
(obsession-compulsion; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(oral; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Testis
(orchialgia; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT 5-HT reuptake inhibitors

Analgesics
Anti-inflammatory agents
Antiasthmatics
Anticonvulsants
Antidepressants
Antihistamines
Antimigraine agents
Antipsychotics
Antipyretics
Anxiety
Anxiolytics
Appetite depressants
Bronchodilators
Canis familiaris
Cardiovascular agents
Cholinergic agonists
Dopamine agonists
Electrolytes
Equus caballus
Felis catus
Ginkgo biloba
Human
Hypnotics and Sedatives
Mental disorder
Muscarinic antagonists
Muscle relaxants
Nervous system stimulants
Pain
Primates
Psychotropics
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Androgen receptors
Epidermal growth factor receptors
Interleukin 1 receptors
Nicotinic receptors
Platelet-activating factor receptors
Potassium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Corticosteroids, biological studies
Phosphatidylserines
Vitamins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Anxiety
(panic disorder; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Mental disorder
(phobia; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phorbol ester; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Mental disorder
(post-traumatic stress disorder; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Ovarian cycle
(premenstrual syndrome; p-hydroxymilnacipran stereoisomers, therapeutic

use, and use with other agents)
IT Biological transport
(reuptake; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(serotonin transporter; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(site 1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(site 2; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(sublingual; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Disease, animal
(temperomandibular disorder; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Headache
(tension headache; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(topical; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(transdermal; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT 5-HT receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 5-HT1A; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT 5-HT receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 5-HT3; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Endothelin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type ETA; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Endothelin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type ETB; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Tachykinin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type NK1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Urethra
(urethral syndrome; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Drug delivery systems
(vaginal; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Pain
(visceral pain syndromes; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Reproductive organ
(vulva, essential vulvodynia; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(κ-opioid; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(σ1-opioid; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(σ2-opioid; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Estrogen receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α1A, α1a; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α1B; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α1D; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α2A; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α2B; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β1; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β2; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(δ-opioid; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(μ-opioid; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT 91-40-7, Fenamic acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fenamates; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT 92623-85-3, Milnacipran
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)
IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine

329736-03-0, Cytochrome P450 3A4 329978-01-0, Cytochrome P450 2C9
330196-64-0, Cytochrome P450 1A2 330589-90-7, Cytochrome P450 2C19
330597-62-1, Cytochrome P450 2D6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT **688320-02-7P, CS 1713 688320-03-8P, CS 1714 688320-04-9P, CS 1814**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT 50-02-2, Dexamethasone 50-22-6, Corticosterone 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 50-55-5, Reserpine 50-78-2, Aspirin 51-63-8, Dextroamphetamine sulfate 52-26-6, Morphinehydrochloride 52-86-8, Haloperidol 53-03-2, Prednisone 53-06-5, Cortisone 53-86-1, Indomethacin 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-42-1, Meperidine 57-53-4, Meprobamate 58-08-2, Caffeine, biological studies 58-25-3, Chlordiazepoxide 58-39-9, Perphenazine 58-46-8, Tetrabenazine 58-94-6, Thiazide 59-92-7, Levodopa, biological studies 61-68-7, Mefenamic acid 62-44-2, Phenacetin 68-88-2, Hydroxyzine 69-23-8, Fluphenazine 72-69-5, Nortriptyline 73-31-4, Melatonin 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-67-8, Ethosuximide 78-44-4, Carisoprodol 83-98-7, Orphenadrine 89-57-6, Mesalamine 99-66-1, Valproic acid 103-90-2, Acetaminophen 113-15-5, Ergotamine 113-45-1, Methylphenidate 113-53-1, Dothiepin 117-89-5, Trifluoperazine 119-36-8, Methylsalicylate 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 129-03-3, Cyproheptadine 134-49-6, Phenmetrazine 138-56-7, Trimethobenzamide 298-46-4, Carbamazepine 300-62-9, Amphetamine 302-40-9, Benactyzine 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 315-72-0, Opipramol 321-64-2, Tacrine 357-56-2, Dextromoramide 357-70-0, Galantamine 359-83-1, Pentazocine 361-37-5, Methysergid(e 364-62-5, Metoclopramide 378-44-9, Betamethasone 427-00-9, Desomorphine 437-38-7, Fentanyl 438-60-8, Protriptyline 439-14-5, Diazepam 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 509-60-4, Dihydromorphine 511-12-6, Dihydroergotamine 525-66-6, Propranolol 532-03-6, Methocarbamol 537-46-2, Methamphetamine 552-94-3, Salsalate 555-30-6, Methyldopa 599-79-1, Sulfasalazine 604-75-1, Oxazepam 634-03-7, Phendimetrazine 739-71-9, Trimipramine 765-30-0, Aminocyclopropane 768-94-5, Amantadine 846-49-1, Lorazepam 846-50-4, Temazepam 1406-18-4, Vitamin E 1622-61-3, Clonazepam 1665-48-1, Metaxalone 1668-19-5, Doxepin 1977-10-2, Loxapine 2016-36-6, Choline salicylate, biological studies 2062-78-4, Pimozide 2152-34-3, Pemoline 3313-26-6, Thiothixene 3861-76-5, Clonitazene 3900-31-0, Fludiazepam 3964-81-6, Azatadine 4205-90-7, Clonidine 4350-09-8, Oxitriptan 4419-39-0, Beclomethasone 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole 5786-21-0, Clozapine 7416-34-4, Molindone 9001-62-1, Lipase 9001-75-6, Pepsin 10262-69-8, Maprotiline 10321-12-7, Propizepine 14028-44-5, Amoxapine 15301-93-6, Tofenacin 15307-79-6, Diclofenac sodium 15574-96-6, Pizotifen 15687-27-1, Ibuprofen 15722-48-2, Olsalazine 17617-23-1, Flurazepam 19794-93-5, Trazodone 19982-08-2, Memantine 21256-18-8, Oxaprozin 21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22232-71-9, Mazindol 22494-42-4, Diflunisal 23047-25-8, Lofepramine 23887-31-2, Clorazepate 24166-13-0, Cloxazolam 24219-97-4, Mianserin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25614-03-3, Bromocriptine 25905-77-5,

Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 27060-91-9, Flutazolam 27203-92-5, Tramadol 28860-95-9, Carbidopa 28911-01-5, Triazolam 28981-97-7, Alprazolam 29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam 31721-17-2, Quinupramine 31842-01-0, Indoprofen 33671-46-4, Clotiazepam 34911-55-2, Bupropion 35941-65-2, Butriptyline 36322-90-4, Piroxicam 36505-84-7, Buspirone 36735-22-5, Quazepam 38194-50-2, Sulindac 41340-25-4, Etodolac 42200-33-9, Nadolol 42408-82-2, Butorphanol 42924-53-8, Nabumetone 43200-80-2, Zopiclone 46817-91-8, Viloxazine 51012-32-9, Tiapride 51022-69-6, Amcinonide 51234-28-7, Benoxaprofen 51322-75-9, Tizanidine 51333-22-3, Budesonide 52485-79-7, Buprenorphine 53608-75-6, Pancrelipase 53648-55-8, Dezocine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 56775-88-3, Zimeldine 59729-33-8, Citalopram 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60762-57-4, Pirlindole 61869-08-7, Paroxetine 68693-11-8, Modafinil 71195-57-8, Bicifadine 71320-77-9, Moclobemide 71620-89-8, Reboxitine 74050-98-9, Ketanserin 74103-06-3, Ketorolac 76584-70-8 78499-27-1, Bermoprofen 79617-96-2, Sertraline 82626-48-0, Zolpidem 83015-26-3, Atomoxetine 83366-66-9, Nefazodone 83928-76-1, Gepirone 84371-65-3, Mifepristone 85650-52-8, Mirtazapine 87051-43-2, Ritanserin 87691-91-6, Tiaspirone 88150-42-9, Amlodipine 89565-68-4, Tropisetron 89796-99-6, Aceclofenac 91374-21-9, Ropinirole 93413-69-5, Venlafaxine 95847-70-4, Ipsapirone 97240-79-4, Topiramate 99614-02-5, Ondansetron 99755-59-6, Rotigotine 102518-79-6, Huperzine A 103628-46-2, Sumatriptan 104632-26-0, Pramipexole 106266-06-2, Risperidone 106650-56-0, Sibutramine 109889-09-0, Granisetron 112924-45-5, Dexanabinol 115956-12-2, Dolasetron 116539-59-4, Duloxetine 120014-06-4, Donepezil 121679-13-8, Naratriptan 123040-69-7, Azasetron 123441-03-2, Rivastigmine 128196-01-0, Escitalopram 129722-12-9, Aripiprazole 132449-46-8, Lesopitron 132539-06-1, Olanzapine 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 144034-80-0, Rizatriptan 146939-27-7, Ziprasidone 148553-50-8, Pregabalin 154323-57-6, Almotriptan 158747-02-5, Frovatriptan 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 181695-72-7, Valdecoxib 198470-84-7, Parecoxib 325715-02-4, Indiplon **686766-17-6 686766-17-6D**, derivs. 688319-36-0, Adomexetine 688319-98-4, Dizatriptan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT 104-47-2, 4-Methoxyphenylacetonitrile 109-89-7, Diethylamine, reactions 51594-55-9, (R)-Epichlorohydrin, reactions **688320-09-4**, **CS 1658**
RL: RCT (Reactant); RACT (Reactant or reagent)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

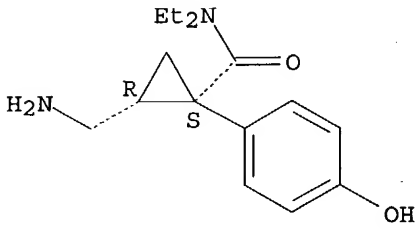
IT 688320-05-0P, CS 1590 688320-06-1P, CS 1608 **688320-07-2P**, **CS 1628 688320-08-3P, CS 1649 688738-11-6P, CS 1665 688738-12-7P, CS 1710**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT **688320-02-7P, CS 1713 688320-03-8P, CS 1714 688320-04-9P, CS 1814**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

RN 688320-02-7 HCAPLUS

CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, monohydrochloride, (1S,2R)- (9CI) (CA INDEX NAME)

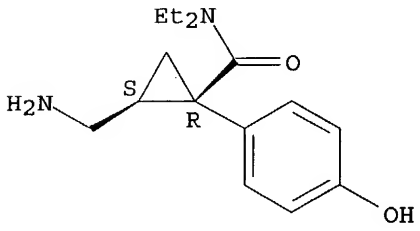
Absolute stereochemistry.



● HCl

RN 688320-03-8 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, monohydrochloride, (1R,2S)- (9CI) (CA INDEX NAME)

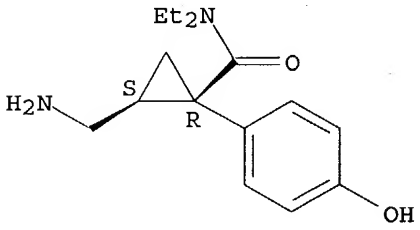
Absolute stereochemistry.



● HCl

RN 688320-04-9 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, monohydrochloride, (1R,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Currently available stereo shown.



● HCl

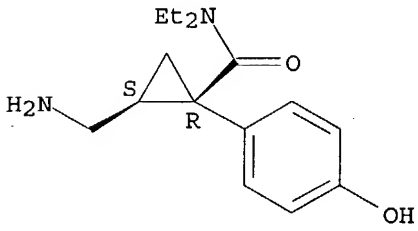
IT **686766-17-6 686766-17-6D**, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

RN 686766-17-6 HCAPLUS

CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)-rel- (9CI) (CA INDEX NAME)

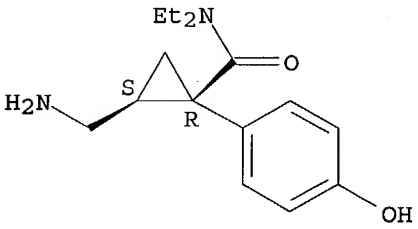
Relative stereochemistry.



RN 686766-17-6 HCAPLUS

CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **688320-09-4, CS 1658**

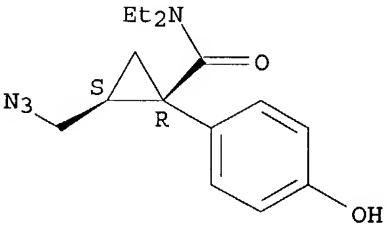
RL: RCT (Reactant); RACT (Reactant or reagent)

(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

RN 688320-09-4 HCAPLUS

CN Cyclopropanecarboxamide, 2-(azidomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **688320-07-2P, CS 1628 688320-08-3P, CS 1649 688738-11-6P, CS 1665 688738-12-7P, CS 1710**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

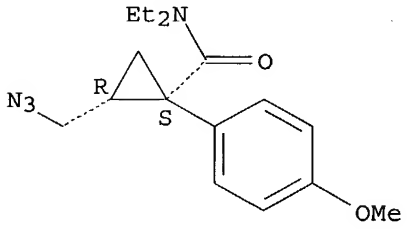
(p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

RN 688320-07-2 HCAPLUS

CN Cyclopropanecarboxamide, 2-(azidomethyl)-N,N-diethyl-1-(4-methoxyphenyl)-,

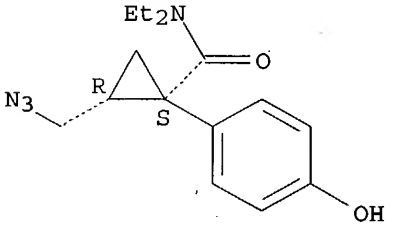
(1S,2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



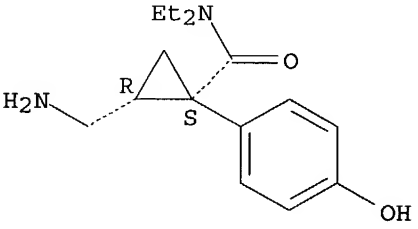
RN 688320-08-3 HCAPLUS
CN Cyclopropanecarboxamide, 2-(azidomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1S,2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



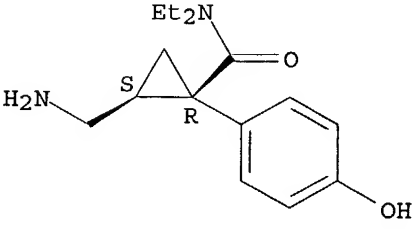
RN 688738-11-6 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1S,2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 688738-12-7 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L21 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:387254 HCAPLUS
DN 140:395521
ED Entered STN: 13 May 2004
TI Pulsatile release compositions of milnacipran
IN Hirsh, Jane; **Rariy, Roman V.**; **Heffernan, Michael**
PA **Collegium Pharmaceutical, Inc., USA**
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-12
ICS A61K009-50; A61K009-22; A61K009-24; A61K031-55; A61K009-16
CC 63-6 (Pharmaceuticals)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004039361	A1	20040513	WO 2003-US33685	20031022 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004121010	A1	20040624	US 2003-690872	20031022 <--
	US 2004132826	A1	20040708	US 2003-690947	20031022 <--
	US 2004122104	A1	20040624	US 2003-691936	20031023 <--
PRAI	US 2002-421640P	P	20021025 <--		
	US 2002-431626P	P	20021205		
	US 2002-431627P	P	20021205		
	US 2002-431861P	P	20021209		
	US 2002-431906P	P	20021209		
	US 2003-443618P	P	20030129		
	US 2003-458994P	P	20030328		
	US 2003-458995P	P	20030328		
	US 2003-459061P	P	20030328		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004039361	ICM	A61K031-12
	ICS	A61K009-50; A61K009-22; A61K009-24; A61K031-55; A61K009-16

AB A once-a-day oral milnacipran pulsatile release composition has been developed that releases the drug in spaced apart 'pulses'. The dosage forms are comprised of dosage units having a different drug release profile, e.g., immediate-release, delayed-release, and enteric-coated units. This dosage form provides in vivo drug plasma levels characterized by Cmax below 3000 ng/mL, preferably below 2000 ng/mL, and most preferably below 1000 ng/mL. These levels help to avoid stimulation of the cholinergic effects on the CNS. The composition allows milnacipran to be delivered over approx. 24 h, when administered to a patient in need, resulting in diminished incidence or decreased intensity of common milnacipran side effects such as sleep disturbance, nausea, vomiting, headache, tremulousness, anxiety, panic attacks, palpitations, urinary retention, orthostatic hypotension, diaphoresis, chest pain, rash, weight gain, back pain, constipation, vertigo, increased sweating, agitation, hot flushes, tremors, fatigue, somnolence, dyspepsia, dysoria, nervousness, dry mouth, abdominal pain, irritability, and insomnia. The milnacipran formulation further comprises at least one

other active compound selected from analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, anxiolytics, sedatives, hypnotics, antipsychotics, bronchodilators, antiasthmatics, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastrointestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics, and anti-narcoleptics.

ST milnacipran pulsatile release dosage form side effect

IT Drug delivery systems
(capsules, pulsatile-release; milnacipran pulsatile-release compns. with reduced side effects)

IT Dissolution
(milnacipran pulsatile-release compns. with reduced side effects)

IT Drug delivery systems
(pulsatile-release; milnacipran pulsatile-release compns. with reduced side effects)

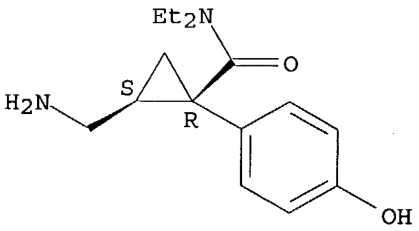
IT 92623-85-3, Milnacipran 101152-94-7, Milnacipran hydrochloride
686766-17-6, F 2782
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(milnacipran pulsatile-release compns. with reduced side effects)

IT **686766-17-6, F 2782**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(milnacipran pulsatile-release compns. with reduced side effects)

RN 686766-17-6 HCAPLUS

CN Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-(4-hydroxyphenyl)-, (1R,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L21 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:511283 HCAPLUS

DN 139:85038

ED Entered STN: 04 Jul 2003

TI Preparation of TNF-α inhibiting hydroxyamic or carboxylic acid functionalized cycloalkanes for the treatment of inflammatory disorders

IN Zhu, Zhaoning; Mazzola, Robert, Jr.; Guo, Zhuyan; Lavey, Brian J.; Sinning, Lisa; Kozlowski, Joseph; McKittrick, Brian; Shih, Neng-Yang

PA Schering Corporation, USA

SO PCT Int. Appl., 179 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C259-00

CC 24-2 (Alicyclic Compounds)
Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003053915	A2	20030703	WO 2002-US40453	20021219
	WO 2003053915	A3	20030918		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU,

ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD,
MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK,
SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

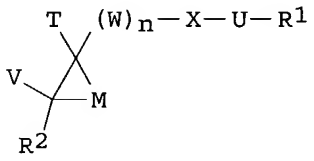
US 2004038941	A1	20040226	US 2002-323511	20021219
EP 1458676	A2	20040922	EP 2002-792429	20021219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2004102418	A1	20040527	US 2003-716890	20031119
PRAI US 2001-342332P	P	20011220		
US 2002-323511	A3	20021219		
WO 2002-US40453	W	20021219		

CLASS

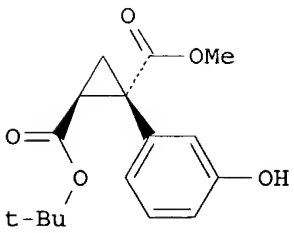
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003053915	ICM	C07C259-00
US 2004102418	ECLA	C07C062/34; C07C069/757; C07C311/29; C07C317/22; C07C323/19; C07D213/30C; C07D213/40B; C07D; C07D213/74; C07D215/14; C07D215/18; C07D215/22C; C07D215/26; C07D215/38B; C07D219/02; C07D233/54C2D2; C07D277/24; C07D277/64; C07D311/58; C07D317/64; C07D401/04+215+213; C07D401/12+215+211; C07D401/12+215+205; C07D401/12+215+207; C07D401/12+215+213; C07D401/12+24B+215; C07D401/12+257+215; C07D413/12+271+215; C07D417/12+277B+215

OS MARPAT 139:85038

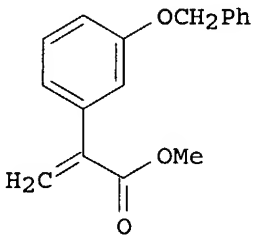
GI



I



II



III

AB This invention relates to compds. of formula I [M = -(C(R30)(R40))m-, wherein m = 1-6; T = substituted alkyl, (un)substituted-cycloalkyl, -heterocycloalkyl, -aryl, etc.; V = (un)substituted alkyl, cycloalkyl, heteroaryl, etc.; R1 = (un)substituted alkyl, alkyne, alkene, cycloalkyl, aryl, etc.; R2 = H, halo, (un)substituted alkyl, cycloalkyl, etc.; U = bond, alkyl, heteroalkyl, heteroatoms; X = (un)substituted alkylene, cycloalkylene, arylene, etc.; W = carboxy, substituted iminomethylene, SO2, SO, etc., wherein n = 0-2; R30 and R40 independently = H or halo, CN, NO2, (un)substituted alkyl, etc.; or R30 and R40 may be taken together with the atom to which they are attached to form C=O, with provisions] or a pharmaceutically acceptable salt, solvate or isomer thereof, which can

be useful for the treatment of diseases or conditions mediated by MMPs, TNF-alpha or combinations thereof. Thus, II was prepared from Me methoxyphenylethanoate with the cyclopropane ring diastereoselectively formed by cyclization of intermediate III with S-carbo-tert-butoxymethyltetrahydrothiophene bromide with subsequent hydrogenation and resolution of enantiomers. Numerous compds. of the invention possessed Ki values of less than 20 nM in a TNF-α convertases (TACE) inhibitory activity assay. As TNF-α inhibitors, I will be useful in treatment of inflammatory disorders.

ST cycloalkane carboxylate prepn tumor necrosis factor alpha inhibitor; hydroxamic cycloalkane prepn matrix metalloproteinase inhibitor; antiinflammatory agent cycloalkane carboxylate prepn

IT Intestine, disease
(Crohn's; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Skin, neoplasm
(T-cell lymphoma; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Granulomatous disease
(Wegener's granulomatosis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Rheumatoid arthritis
(adult-onset Still's disease; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Respiratory distress syndrome
(adult; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Nose, disease
(allergic rhinitis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Spinal column, disease
(ankylosing spondylitis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Infection
(bacterial, myco-; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Bronchi, disease
(bronchitis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Lung, disease
(bronchopulmonary dysplasia; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Lung, disease
(chronic obstructive; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Intestine, disease
(colitis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Eye, disease
(cornea, ulcer; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix

metalloproteinases)
IT Radiation
(damage; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Heart, disease
(failure; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Lung, disease
(fibrosis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Gingiva, disease
(gingivitis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Kidney, disease
(glomerulonephritis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Transplant and Transplantation
(graft-vs.-host reaction; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Heart, disease
(infarction; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Intestine, disease
(inflammatory; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Reperfusion
(injury; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Kidney, disease
(ischemia; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Kidney, disease
(nephritis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Anti-inflammatory agents
(nonsteroidal; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Periodontium, disease
(periodontitis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT Muscle, disease
(polymyositis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT AIDS (disease)
Acute-phase response
Alcoholism
Allergy
Allergy inhibitors
Angiogenesis

Angiogenesis inhibitors
Anorexia
Anti-AIDS agents
Anti-inflammatory agents
Anti-ischemic agents
Antiasthmatics
Antibacterial agents
Anticoagulants
Antidiabetic agents
Antiglaucoma agents
Antimalarials
Antipyretics
Antirheumatic agents
Antitumor agents
Asthma
Autoimmune disease
Cachexia
Cachexia
Cardiovascular agents
Cardiovascular system, disease
Coagulation
Dermatomyositis
Diabetes mellitus
Drug delivery systems
Fever and Hyperthermia
Glaucoma (disease)
Hemorrhage
Hepatitis
Inflammation
Inflammation
Malaria
Meningitis
Multiple sclerosis
Neoplasm
Osteoarthritis
Osteoarthritis
Osteoporosis
Periodontium, disease
Psoriasis
Rheumatoid arthritis
Sarcoidosis
Sarcoidosis
Shock (circulatory collapse)
Sjogren's syndrome
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Tumor necrosis factor receptors
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Cycloalkanes
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Arthritis
(psoriatic arthritis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor

alpha and/or matrix metalloproteinases)

IT Eye, disease
(retinopathy; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Connective tissue, disease
(scleroderma; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Sepsis
(sepsis syndrome; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Shock (circulatory collapse)
(septic; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Brain, disease
(stroke; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Lupus erythematosus
(systemic; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT Blood vessel, disease
(vasculitis; preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556105-10-3P 556105-31-8P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556105-09-0P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556105-18-1P 556105-21-6P 556105-25-0P 556107-00-7P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556105-11-4P 556105-12-5P 556105-13-6P 556105-14-7P 556105-15-8P
556105-16-9P 556105-17-0P 556105-19-2P 556105-20-5P 556105-22-7P
556105-23-8P 556105-24-9P 556105-26-1P 556105-27-2P 556105-28-3P
556105-29-4P 556105-30-7P 556105-32-9P 556105-33-0P 556105-34-1P
556105-35-2P 556105-36-3P 556105-37-4P 556105-38-5P 556105-40-9P
556105-41-0P 556105-42-1P 556105-43-2P 556105-44-3P 556105-45-4P
556105-46-5P 556105-47-6P 556105-48-7P 556105-49-8P 556105-50-1P
556105-51-2P 556105-52-3P 556105-53-4P **556105-54-5P**
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556107-59-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556107-60-9P 556107-62-1P 556107-63-2P 556107-65-4P 556107-66-5P
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556107-78-9P 556107-80-3P 556107-82-5P 556107-84-7P 556107-86-9P
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556109-34-3P 556109-36-5P 556109-38-7P 556109-40-1P 556109-42-3P
556109-44-5P 556109-46-7P 556109-48-9P 556109-50-3P 556109-53-6P
556109-55-8P 556109-59-2P 556109-61-6P 556109-63-8P 556109-65-0P

556109-67-2P 556109-69-4P 556109-71-8P 556109-72-9P 556109-73-0P
556109-74-1P 556109-75-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556105-39-6P
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 62-53-3, Aniline, reactions 67-63-0, 2-Propanol, reactions 98-68-0, p-Methoxyphenylsulfonylchloride 100-39-0, Benzyl bromide 107-20-0, Chloroacetaldehyde 109-01-3, 1-Methylpiperazine 123-75-1, Pyrrolidine, reactions 524-38-9 613-45-6, 2,4-Dimethoxybenzaldehyde 623-05-2 764-39-6, 2-Pentenal 824-94-2 1777-82-8, 2,4-Dichlorobenzyl alcohol 2607-03-6 2788-84-3 4224-69-5, Methyl 2-(bromomethyl)acrylate 5544-60-5, 4-Benzyloxybenzylbromide 6313-54-8 6793-92-6 13331-27-6, m-Nitrophenylboronic acid 13922-41-3, 1-Naphthylboronic acid 18927-05-4 53087-13-1 56441-69-1 77406-65-6 119778-64-2 223438-10-6 288399-19-9, 4-(Chloromethyl)-2-methylquinoline 556104-98-4 556110-00-0 556110-01-1 556110-02-2 556110-03-3 556110-04-4 556110-05-5 556110-06-6 556110-07-7 556110-08-8 556110-09-9 556110-10-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

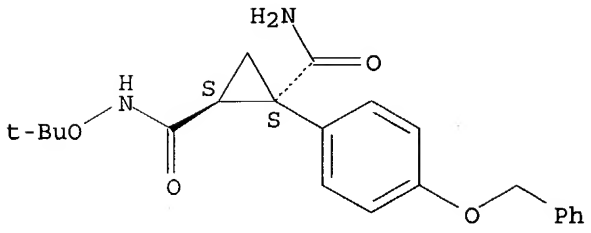
IT 42058-59-3P 62969-42-0P 196395-02-5P 216067-79-7P 519146-86-2P 556109-76-3P 556109-77-4P 556109-78-5P 556109-79-6P 556109-80-9P 556109-81-0P 556109-82-1P 556109-83-2P 556109-84-3P 556109-85-4P 556109-86-5P 556109-87-6P 556109-89-8P 556109-90-1P 556109-91-2P 556109-92-3P 556109-93-4P 556109-94-5P 556109-95-6P 556109-97-8P 556109-98-9P 556109-99-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556109-88-7P 556109-96-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT **556105-54-5P 556109-05-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

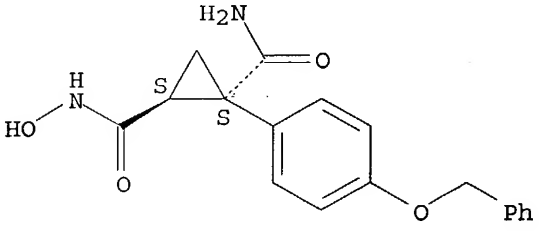
RN 556105-54-5 HCAPLUS
CN 1,2-Cyclopropanedicarboxamide, N2-(1,1-dimethylethoxy)-1-[4-(phenylmethoxy)phenyl]-, (1S,2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 556109-05-8 HCAPLUS
CN 1,2-Cyclopropanedicarboxamide, N2-hydroxy-1-[4-(phenylmethoxy)phenyl]-, (1S,2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



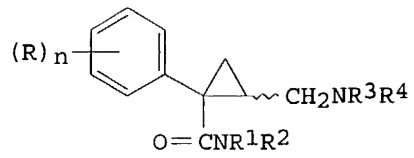
L21 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:639722 HCAPLUS
DN 115:239722
ED Entered STN: 29 Nov 1991
TI 1-Aryl-2-(aminomethyl)cyclopropanecarboxyamide derivatives for treatment of cerebral ischemia
IN Mochizuki, Daisuke
PA Toyo Jozo Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K031-16
ICS A61K031-165; A61K031-40; A61K031-435; A61K031-495; A61K031-535; C07D207-06; C07D295-04; C07D295-18
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 03056415	A2	19910312	JP 1989-191064	19890724
PRAI JP 1989-191064		19890724		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
JP 03056415	ICM	A61K031-16
	ICS	A61K031-165; A61K031-40; A61K031-435; A61K031-495; A61K031-535; C07D207-06; C07D295-04; C07D295-18

OS MARPAT 115:239722
GI



I

AB Pharmaceuticals preventing cerebral cell damages in ischemia contain I where R = H, halo, lower alkyl, etc.; n = 1, 2; R1 = H, lower alkyl, (un)substituted Ph, etc.; R2 = H, lower alkyl, etc.; R3 = H, alkanoyl, etc.; R4 = H, lower alkyl, a part of heterocyclic ring. Thirty-six I compds. are claimed. Thus, an injection solution was prepared by dissolving 1-phenyl-1-diethylaminocarbonyl-2-aminomethylcyclopropane (Z)-HCl (1.0 g) in 1L H2O, adjusting pH to 6-7 with 1N NaOH, sterilizing, and charging ampuls with 5 mL each.

ST brain ischemia cyclopropane deriv

IT Ischemia
(cerebral, treatment of, aryl(aminomethyl)cyclopropane carboxamide derivs. for)

IT 86181-04-6 86181-05-7 86181-07-9 86181-09-1 86181-11-5
86181-12-6 86181-13-7 86181-14-8 86181-15-9 86181-16-0
86181-17-1 86181-18-2 86181-19-3 86181-20-6
101152-94-7 105310-24-5 105310-25-6 105310-34-7 105310-35-8
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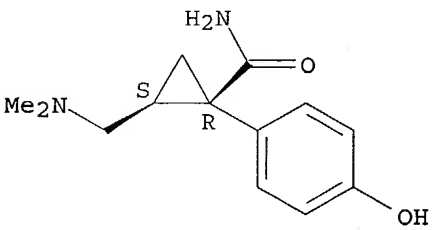
136091-02-6 136091-03-7 136091-04-8 136091-05-9 136091-06-0
136091-07-1 136091-08-2 136091-09-3 136091-10-6 136091-11-7
136091-12-8 136091-13-9 **136091-14-0** 136091-15-1
RL: BIOL (Biological study)
(pharmaceutical containing, for cerebral ischemia treatment)

IT **86181-17-1 86181-18-2 86181-19-3**
136090-91-0 136090-92-1 136090-93-2
136090-95-4 136091-14-0
RL: BIOL (Biological study)
(pharmaceutical containing, for cerebral ischemia treatment)

RN 86181-17-1 HCAPLUS

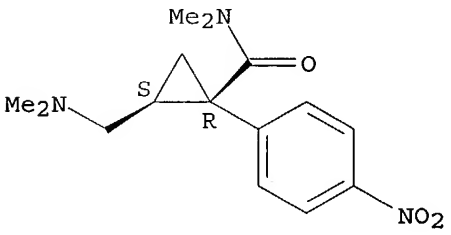
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-1-(4-hydroxyphenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 86181-18-2 HCAPLUS
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-N,N-dimethyl-1-(4-nitrophenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

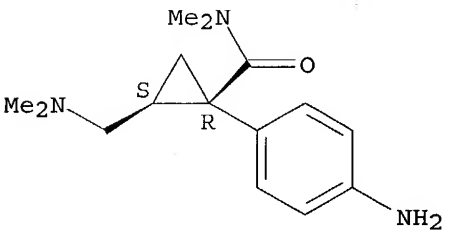
Relative stereochemistry.



● HCl

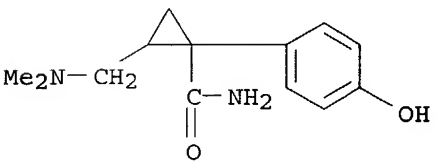
RN 86181-19-3 HCAPLUS
CN Cyclopropanecarboxamide, 1-(4-aminophenyl)-2-[(dimethylamino)methyl]-N,N-dimethyl-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

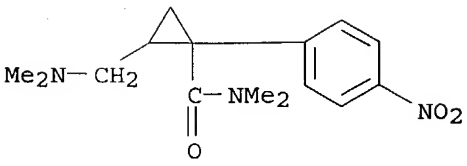


● HCl

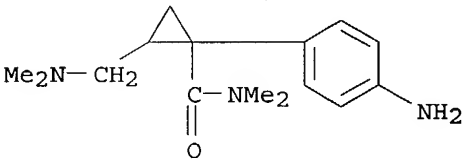
RN 136090-91-0 HCAPLUS
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-1-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



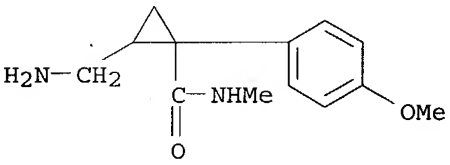
RN 136090-92-1 HCAPLUS
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-N,N-dimethyl-1-(4-nitrophenyl)- (9CI) (CA INDEX NAME)



RN 136090-93-2 HCAPLUS
CN Cyclopropanecarboxamide, 1-(4-aminophenyl)-2-[(dimethylamino)methyl]-N,N-dimethyl- (9CI) (CA INDEX NAME)

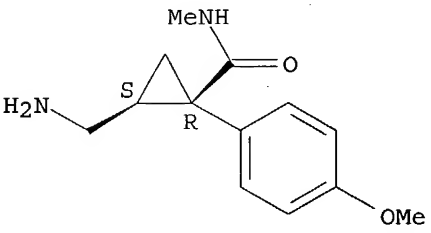


RN 136090-95-4 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-N-methyl- (9CI) (CA INDEX NAME)



RN 136091-14-0 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-N-methyl-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

L21 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1983:422001 HCAPLUS
DN 99:22001
ED Entered STN: 12 May 1984
TI 1-Aryl-2-(aminomethyl)cyclopropanecarboxamides (Z) and their use as medicines in the treatment of disorders of the central nervous system
IN Mouzin, Gilbert; Cousse, Henri; Bonnaud, Bernard; Morre, Michel; Stenger,

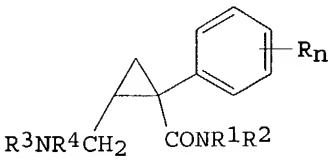
Antoine
PA Fabre, Pierre, S. A., Fr.
SO Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DT Patent
LA French
IC C07C103-28; C07C103-29; C07C103-76; C07D295-14; C07D295-18; A61K031-165; A61K031-395
CC 24-2 (Alicyclic Compounds)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 68999	A1	19830105	EP 1982-401129	19820621
	EP 68999	B1	19850522		
	R: AT, BE, CH, DE, GB, IT, LI, LU, NL, SE				
	FR 2508035	A1	19821224	FR 1981-12312	19810623
	FR 2508035	B1	19840629		
	ES 512842	A1	19830301	ES 1982-512842	19820604
	AT 13422	E	19850615	AT 1982-401129	19820621
	AU 8285086	A1	19830106	AU 1982-85086	19820622
	AU 550774	B2	19860410		
	US 4478836	A	19841023	US 1982-390810	19820622
	CA 1202639	A1	19860401	CA 1982-405651	19820622
	JP 58004752	A2	19830111	JP 1982-109097	19820623
	JP 63023186	B4	19880516		
	ZA 8204453	A	19830427	ZA 1982-4453	19820623
PRAI	FR 1981-12312	A	19810623		
	EP 1982-401129	A	19820621		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES		
EP 68999	IC	C07C103-28IC	C07C103-29IC	C07C103-76IC
		C07D295-14IC	C07D295-18IC	A61K031-165IC
		A61K031-395		

GI

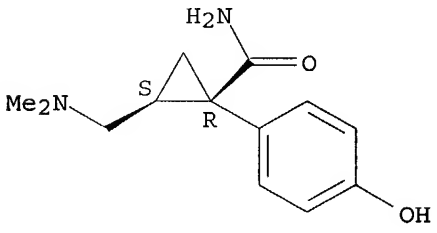


I

AB Amides I (n = 1,2; R = H, halo, alkyl, alkoxy, OH, NO2, NH2; R1 and R2 are H, alkyl, aryl, alkylaryl, or NR1R2 form a heterocycle; R3 and R4 are H, alkyl, or NR3R4 form a heterocycle), useful as central nervous system agents (no data), were prepared 2-[(Dimethylamino)methyl]-1-phenylcyclopropanecarbonyl chloride hydrochloride reacted with NH3 to give I (n = 1, R = R1 = R2 = H, R3 = R4 = Me).
ST aminomethylcyclopropanecarboxamide prepn CNS agent; cyclopropanecarboxamide aminomethyl
IT Central nervous system agents
((aminomethyl)cyclopropanecarboxamides)
IT 64-04-0 75-04-7, reactions 104-86-9 106-47-8, reactions 124-40-3, reactions 7664-41-7, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation by, of cyclopropanecarbonyl chloride derivative)
IT 86181-03-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and amidation of)
IT 86181-02-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with thionyl chloride)
IT 86181-04-6P 86181-05-7P 86181-07-9P 86181-09-1P 86181-11-5P
86181-12-6P 86181-13-7P 86181-14-8P 86181-15-9P 86181-16-0P
86181-17-1P 86181-18-2P 86181-19-3P
86181-20-6P **86181-21-7P** 101152-94-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT 69160-76-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(saponification of)
IT **86181-17-1P 86181-18-2P 86181-19-3P**
86181-21-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 86181-17-1 HCAPLUS
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-1-(4-hydroxyphenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

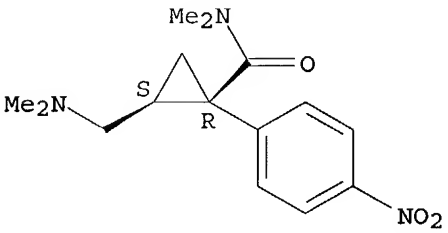
Relative stereochemistry.



● HCl

RN 86181-18-2 HCAPLUS
CN Cyclopropanecarboxamide, 2-[(dimethylamino)methyl]-N,N-dimethyl-1-(4-nitrophenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

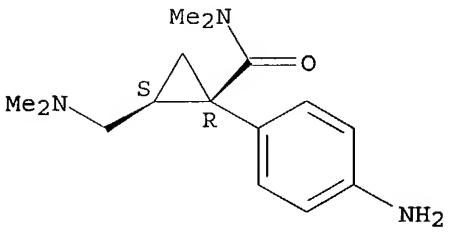
Relative stereochemistry.



● HCl

RN 86181-19-3 HCAPLUS
CN Cyclopropanecarboxamide, 1-(4-aminophenyl)-2-[(dimethylamino)methyl]-N,N-dimethyl-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

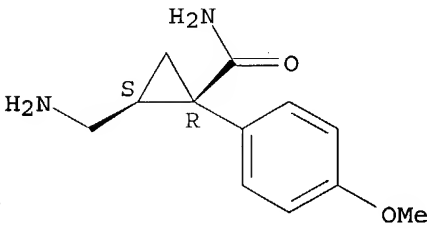
Relative stereochemistry.



● HCl

RN 86181-21-7 HCAPLUS
CN Cyclopropanecarboxamide, 2-(aminomethyl)-1-(4-methoxyphenyl)-, monohydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

=> fil uspatfull
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REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

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>>> publication date for all the US publications for an invention <<<
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>>> /PK, etc. <<<

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>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l25 bib abs kwic hitrn tot

L25 ANSWER 1 OF 9 USPATFULL on STN
AN 2004:291750 USPATFULL
TI Multiparticulate compositions of milnacipran for oral administration
IN Hirsh, Jane, Wellesley, MA, UNITED STATES
Fleming, Alison B., Marshfield, MA, UNITED STATES
Rariy, Roman V., Allston, MA, UNITED STATES
PA Collegium Pharmaceutical, Inc. (U.S. corporation)
PI US 2004228830 A1 20041118
AI US 2004-766124 A1 20040128 (10)
PRAI US 2003-490060P 20030724 (60)
US 2003-468470P 20030506 (60)
US 2003-458993P 20030328 (60)
US 2003-443618P 20030129 (60)
US 2003-443237P 20030128 (60)
DT Utility
FS APPLICATION
LREP PATREA L. PABST, PABST PATENT GROUP LLP, 400 COLONY SQUARE, SUITE 1200, ATLANTA, GA, 30361
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1252
AB A multiparticulate milnacipran composition for oral administration has been developed. The formulation is made by complexing milnacipran with an ion-exchange resin in the form of small particles, typically less than 150 microns. Multiparticulate formulations may be any one or more of the following types of particles are formulated into a final dosage form: immediate release particles, prepared by coating drug-containing particles with the polymer that is insoluble in the neutral medium of saliva, but dissolves in the acid environment of the stomach; enteric coated particles, prepared by coating drug-containing particles with the polymer that is insoluble in the acidic environment of the stomach but dissolves in the neutral environment of the small intestines; extended release particles, prepared by coating drug-containing particles with a polymer that forms water insoluble but water permeable membrane; enteric coated-extended release particles, prepared by coating extended release drug particles with a second, enteric coating; delayed release particles, prepared by coating drug-containing particles with a polymer that is insoluble in the acidic environment of the stomach and the environment of the upper small intestines, but dissolves in the lower small intestines or upper large intestines. The various drug-containing particles described above can be further formulated into a number of different final dosage forms including, but not limited to, a liquid, liquid suspension, gel, capsule, soft gelatin capsule, tablet, chewable tablet, crushable tablet, rapidly dissolving tablet, or unit of use sachet or capsule for reconstitution.

CLM What is claimed is:
. . . The milnacipran composition of claim 1, wherein the milnacipran is in

the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (**F2782**).

L25 ANSWER 2 OF 9 USPATFULL on STN
AN 2004:209900 USPATFULL
TI Use of the dextrogyral enantiomer of milnacipran for the preparation of a drug
IN Deregnaucourt, Jean, Paris, FRANCE
Grosse, Richard, Gidy, FRANCE
PI US 2004162334 A1 20040819
AI US 2003-453574 A1 20030603 (10)
PRAI FR 2003-1849 20030214
DT Utility
FS APPLICATION
LREP THE FIRM OF HUESCHEN AND SAGE, 500 COLUMBIA PLAZA, 350 EAST MICHIGAN AVENUE, KALAMAZOO, MI, 49007
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 2004
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention concerns the use of a mixture of enantiomers enriched in the dextrogyral enantiomer of milnacipran and/or of at least one of its metabolites, as well as their pharmaceutically-acceptable salts, for the preparation of a drug intended to prevent or to treat disorders that can be managed by double inhibition of serotonin (5-HT) and norepinephrine (NE) reuptake, while limiting the risks of cardiovascular disturbances and/or organ and/or tissue toxicity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0037] the hydrochloride of Z-(para-hydroxyphenyl)-1 diethylaminocarbonyl-1 aminomethyl-2 cyclopropane (**F2782**): ##STR4##
SUMM . . . active metabolite. In a more preferable manner, this is the dextrogyral enantiomer of the hydrochloride of Z-(para-hydroxyphenyl)-1 diethylaminocarbonyl-1 aminomethyl-2 cyclopropane (**F2782**). The term "active metabolite" is understood to designate a derivative of milnacipran metabolised in vitro or in vivo and having the capacity to inhibit reuptake of serotonin and of norepinephrine; preferentially, these are **F2782**, F2941, F2800, F1612 and F1567. For the purposes of the present invention, the active metabolites in vivo described and claimed. . .
SUMM . . . a mixture of enantiomers preferentially enriched in the dextrogyral enantiomer of at least one metabolite of Milnacipran, preferentially chosen among **F2782**, F2941, F2800, F1612 and F1567, as well as their pharmaceutically-acceptable salts, for the preparation of a drug intended to prevent. . .
SUMM . . . in the dextrogyral enantiomer, preferentially the substantially-pure F2595 enantiomer, and at least one of its active metabolites, preferentially chosen among **F2782**, F2941, F2800, F1612 and F1567, preferentially enriched in the dextrogyral enantiomer, for the preparation of a drug intended to prevent. . .
CLM What is claimed is:
. . . is selected among: the hydrochloride of Z-phenyl-1-aminomethyl-2-cyclopropane carboxylic acid (F1567), phenyl-3 methylene-3-4-pyrrolidone-3 (F1612), the hydrochloride of Z-(para-hydroxyphenyl)-1 diethylaminocarbonyl-1 aminomethyl-2 cyclopropane (**F2782**), the oxalic acid of Z-phenyl-1-ethylamino carbonyl-1 aminomethyl-2 cyclopropane (F2800), and the hydrochloride of Z-phenyl-1 aminocarbonyl-1 aminomethyl-2 cyclopropane (F2941).

8. Use according to claim 7, characterised in that the said metabolite

is the chlorhydrate of Z-(para-hydroxyphenyl)-1-diethylaminocarbonyl-1 aminomethyl-2-cyclopropane (**F2782**).

11. Use according to claim 1, characterised in that the said mixture of enantiomers is substantially pure in the hydrochloride of Z-(para-hydroxyphenyl)-1-diethylaminocarbonyl-1-aminomethyl-2-cyclopropane (**F2782**).

IT 92623-85-3, Milnacipran 96847-54-0 96847-55-1 105310-34-7, F 2941 105310-35-8, F 2800 **686766-17-6**, F2782
(dextrogyral enantiomer of milnacipran as double inhibitors of serotonin and norepinephrine reuptake)
IT **686766-17-6**, F2782
(dextrogyral enantiomer of milnacipran as double inhibitors of serotonin and norepinephrine reuptake)

L25 ANSWER 3 OF 9 USPATFULL on STN
AN 2004:185018 USPATFULL
TI Stereoisomers of p-hydroxy-milnacipran, and methods of use thereof
IN Rariy, Roman V., Allston, MA, UNITED STATES
Heffernan, Michael, Hingham, MA, UNITED STATES
Buchwald, Stephen L., Newton, MA, UNITED STATES
Swager, Timothy M., Newton, MA, UNITED STATES
PI US 2004142904 A1 20040722
AI US 2003-691465 A1 20031022 (10)
PRAI US 2003-445142P 20030205 (60)
US 2002-423062P 20021101 (60)
US 2002-421640P 20021025 (60)
DT Utility
FS APPLICATION
LREP FOLEY HOAG, LLP, PATENT GROUP, WORLD TRADE CENTER WEST, 155 SEAPORT BLVD, BOSTON, MA, 02110
CLMN Number of Claims: 44
ECL Exemplary Claim: 1
DRWN 63 Drawing Page(s)
LN.CNT 4076
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates generally to the enantiomers of para-hydroxy-milnacipran or congeners thereof. Biological assays revealed that racemic para-hydroxy-milnacipran is approximately equipotent in inhibiting serotonin and norepinephrine uptake (IC.sub.50=28.6 nM for norepinephrine, IC.sub.50=21.7 nM for serotonin). Interestingly, (+)-para-hydroxy-milnacipran is a more potent inhibitor of norepinephrine uptake than serotonin uptake (IC.sub.50=10.3 nM for norepinephrine, IC.sub.50=22 nM for serotonin). In contrast, (-)-para-hydroxy-milnacipran is a more potent inhibitor of serotonin uptake compared to norepinephrin uptake (IC.sub.50=88.5 nM for norepinephrine, IC.sub.50=40.3 nM for serotonin). The invention also relates to salts and prodrug forms of the aforementioned compounds. In certain embodiments, the compounds of the present invention and a pharmaceutically acceptable excipient are combined to prepare a formulation for administration to a patient. Finally, the present invention relates to methods of treating mammals suffering from various afflictions, e.g., depression, chronic pain, or fibromyalgia, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DRWD [0017] FIG. 6 depicts a .sup.1H NMR spectrum of **CS1628**.
DRWD [0018] FIG. 7 depicts a .sup.13C NMR spectrum of **CS1628**.
DRWD [0019] FIG. 8 depicts a .sup.1H NMR spectrum of **CS1649**.
DRWD [0020] FIG. 9 depicts a .sup.13C NMR spectrum of **CS1649**.

DRWD [0021] FIG. 10 depicts a HPLC chromatogram of **CS1665** (HPLC Conditions: 10% to 95% acetonitrile within 8 min; 2 min at 95%, LM with 0.1% TFA, Flow: 2.0 mL/min,. . .

DRWD [0022] FIG. 11 depicts a mass spectrum of **CS1665.**

DRWD [0023] FIG. 12 depicts a .sup.1H NMR spectrum of **CS1665.**

DRWD [0024] FIG. 13 depicts a 1.sup.3C NMR spectrum of **CS1665.**

DRWD [0025] FIG. 14 depicts a HPLC chromatogram of **CS1710** (HPLC Conditions: 10% to 95% acetonitrile within 8 min; 2 min at 95%, LM with 0.1% TFA, Flow: 2.0 mL/min,. . .

DRWD [0026] FIG. 15 depicts a mass spectrum of **CS1710.**

DRWD [0027] FIG. 16 depicts a .sup.1H NMR spectrum of **CS1710.**

DRWD [0028] FIG. 17 depicts a .sup.13C NMR spectrum of **CS1710.**

DRWD [0029] FIG. 18 depicts a HPLC chromatogram of **CS1713** (HPLC Conditions: 10% to 95% acetonitrile within 8 min; 2 min at 95%, LM with 0.1% TFA, Flow: 2.0mL/min, Saule: Zorbax. . .

DRWD [0030] FIG. 19 depicts a mass spectrum of **CS1713.**

DRWD [0031] FIG. 20 depicts a .sup.1H NMR spectrum of **CS1713.**

DRWD [0032] FIG. 21 depicts a .sup.13C NMR spectrum of **CS1713.**

DRWD [0033] FIG. 22 depicts a HPLC chromatogram of **CS1714** (HPLC Conditions: 10% to 95% acetonitrile within 8 min; 2 min at 95%, LM with 0.1% TFA, Flow: 2.0 mL/min,. . .

DRWD [0034] FIG. 23 depicts a mass spectrum of **CS1714.**

DRWD [0035] FIG. 24 depicts a .sup.1H NMR spectrum of **CS1714.**

DRWD [0036] FIG. 25 depicts a .sup.13C NMR spectrum of **CS1714.**

DRWD [0037] FIG. 26 depicts a HPLC chromatogram of **CS1814** (racemic p-Hydroxy-Milnacipran Hydrochloride; HPLC Conditions: 10% to 95% acetonitrile within 8 min; 2 min at 95%, LM with 0.1% TFA,. . .

DRWD [0038] FIG. 27 depicts a LC/MS chromatogram of **CS1814.**

DRWD [0039] FIG. 28 depicts a mass spectrum of selected peaks from the LC/MS chromatogram of **CS1814.**

DRWD [0040] FIG. 29 depicts a mass spectrum of a peak from the LC/MS chromatogram of **CS1814.**

DRWD [0041] FIG. 30 depicts a .sup.1H NMR spectrum of **CS1814.**

DRWD [0042] FIG. 31 depicts a .sup.13C NMR spectrum of **CS1814.**

DRWD [0043] FIG. 32 depicts biological activity data for **CS1814** in assays using receptors from human (hum) and rat.

DRWD [0044] FIG. 33 depicts biological activity data for **CS1814** in assays using receptors from human (hum), mouse, guinea pig (gp), syrian hamster (syh), and rat.

DRWD [0045] FIG. 34 depicts biological activity data for **CS1814** in assays using receptors from human (hum) and rat.

DRWD [0046] FIG. 35 depicts biological activity data for **CS1814** in assays using receptors from human (hum).

DRWD [0050] FIG. 39 depicts a graph of % inhibition of Norephinephrine Transporter (NET) by **CS1814** (Vial #1).

DRWD [0051] FIG. 40 depicts a graph of % inhibition of Serotonin Transporter (SERT) by **CS1814** (Vial #1).

DRWD [0052] FIG. 41 depicts biological activity data for **CS1713** (Vial #2) and **CS1714** (Vial #3).

DRWD [0053] FIG. 42 depicts biological activity data for **CS1713** (Vial #2) and **CS1714** (Vial #3).

DRWD [0054] FIG. 43 depicts biological activity data for **CS1713** (Vial #2) and **CS1714** (Vial #3).

DRWD [0055] FIG. 44 depicts biological activity data for **CS1713** (Vial #2), **CS1714** (Vial #3), and **CS1814** (Vial#1).

DRWD [0056] FIG. 45 depicts biological activity data for **CS1713** (Vial #2), **CS1714** (Vial #3), and **CS1814** (Vial#1).

DRWD [0057] FIG. 46 depicts biological activity data for **CS1714** (Vial #3).

DRWD [0058] FIG. 47 depicts a graph of % inhibition of Norepinephrine Uptake by **CS1814** (CEL-1) and Desipramine.

DRWD [0059] FIG. 48 depicts a graph of % inhibition of Serotonin Uptake by **CS1814** (CEL-1) and Fluoxetine.

DRWD [0060] FIG. 49 depicts a graph of % inhibition of Norepinephrine Transporter by **CS1713** (CEL-3) and Desipramine.

DRWD [0061] FIG. 50 depicts a graph of % inhibition of Serotonin Transporter by CS1713 (CEL-3) and GBR-12909.

DRWD [0062] FIG. 51 depicts a graph of % inhibition of Norepinephrine Uptake by CS1713 (CEL-3) and Desipramine.

DRWD [0063] FIG. 52 depicts a graph of % inhibition of Serotonin Uptake by CS1713 (CEL-3) and Fluoxetine.

DRWD [0064] FIG. 53 depicts a graph of % inhibition of Norepinephrine Transporter by **CS1714** (CEL-5) and Desipramine.

DRWD [0065] FIG. 54 depicts a graph of % inhibition of Serotonin Transporter by CS1714 (CEL-5) and GBR-12909.

DRWD [0066] FIG. 55 depicts a graph of % inhibition of Norepinephrine Uptake by CS1714 (CEL-5) and Desipramine.

DRWD [0067] FIG. 56 depicts a graph of % inhibition of Serotonin Uptake by CS1714 (CEL-5) and Fluoxetine.

DRWD [0070] FIG. 59 depicts a summary of significant primary results for CS1814.

DRWD [0071] FIG. 60 depicts a summary of significant primary results for CS1713 (Vial #2) and **CS1714** (Vial #3).

DRWD [0072] FIG. 61 depicts a summary of significant primary results for CS1814 (Vial #1), **CS1713** (Vial #2) and **CS1714** (Vial #3).

DRWD [0073] FIG. 62 depicts a summary of secondary results for **CS1814** (Vial #1), **CS1713** (Vial #2) and **CS1714** (Vial #3).

DETD . . . Compounds refered to in the specification and figures are identified using a six-character alpha-numeric code. For example, racemic p-hydroxy-milnacipran is **CS1814.** In certain instances, the six-character alpha-numeric code is followed by forward slash and a number. The forward slash followed by a number indicates the batch from which the data was taken. For example, **CS1814**/1 indicates that the compound is p-hydroxy-milnacipran and the data was taken from batch 1.

DETD . . . and diethylamine, furnished CS1608 and the corresponding enantiomer, respectively. Conversion of the primary alcohols CS1608 and CS1609 to the azides **CS1628** and C1648 was accomplished in a pot procedure by in situ generation of the corresponding mesylates followed by nucleophilic displacement. . . group was carried out in the presence of borontribromide at -30° C. for 48 h and produced the deprotected phenols **CS1649** and **CS1658** in 66% yield. Final reduction of the azide moiety in **CS1649** and CS1658 under standard reaction conditions furnished the desired target compounds **CS1665** and **CS1710.** Preparation of the corresponding hydrochloric acid salts was accomplished by using hydrochloric acid in dioxane and subsequent removal of the. . .

DETD [0137] The results from the biological testing of **CS1814**, CS1713, **CS1714**, and various reference compounds are presented in FIGS. 32-62. **CS1814** (Vial #1), **CS1713** (Vial #2), and **CS1714** (Vial #3) were evaluated in various radioligand binding assays, and for inhibition of CYP450 3A4 at initial concentrations of 10. . .

DETD [0138] In addition, **CS1713** (Vial #2), **CS1714** (Vial #3), and **CS1814** (Vial #1) were evaluated for inhibition of cellular Serotonin and Norepinephrine Uptake. As depicted in FIG. 61, CS1814 (Vial #1) is approximately equipotent in inhibiting serotonin and norepinephrine uptake (IC.sub.50=28.6 nM for norepinephrine, IC.sub.50=21.7 nM for serotonin). Interestingly, CS1713 (Vial #2) is a more potent inhibitor of norepinephrine uptake than serotonin uptake (IC.sub.50=10.3 nM for norepinephrine, IC.sub.50=22 nM for serotonin). In contrast, **CS1714** (Vial #3) is a more potent inhibitor of serotonin uptake compared to norepinephrin uptake (IC.sub.50=88.5 nM for norepinephrine, IC.sub.50=40.3 nM for serotonin). The fact that **CS1713** (Vial #2) is a more potent

inhibitor of norepinephrine uptake would render it a superior therapeutic agent for treating diseases linked to norepinephrine uptake. In addition, the **CS1714** (Vial #3) would useful for treating conditions requiring selective inhibition of serotonin uptake.

DETD [0139] Importantly, no cytotoxicity was observed for **CS1713** (Vial #2), **CS1714** (Vial #3), or **CS1814** (Vial #1) at 10 μM. In addition, **CS1814** (Vial #1) is a selective inhibitor of norepinephrine and serotonin receptors. The fact that CS1814 generally does not bind well to other receptors, as depicted in FIGS. 32 and 33, substantially reduces the risk of negative side effects associated with administering the compound to a patient. Therefore, it is likely that **CS1713** and **CS1714** will not have detrimental side effects.

DETD . . . 1-(4Methoxy-phenyl9-3 -oxa-bicyclo[3.1.0]hexan-2-one (CS1591), 1S, 2R 2-Hydroxymethyl-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid diethylamide (CS1608), 1R, 2S 2-Hydroxymethyl-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid diethylamide (CS1609), 1S, 2R 2-Azidomethyl-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid diethylamide (**CS1628**), 1R, 2S 2-Azidomethyl-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid diethylamide (CS1648), 1S, 2R 2-Azidomethyl-1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid diethylamide (**CS1649**), 1R, 2S 2-Azidomethyl-1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid diethylamide (**CS1658**), 1S, 2R 2-Aminomethyl-1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid diethyl amide (**CS1665**), 1R, 2S 2-Aminomethyl-1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid diethyl amide (**CS1710**), and racemic 2-Aminomethyl-1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid diethyl amide (**CS1814**).

DETD [0280] In certain embodiments, the combination therapy comprises CS1713 and a SSRI. In certain embodiments, the combination therapy comprises **CS1713** and a SNRI. In certain embodiments, the combination therapy comprises **CS1713**, a SSRI, and a SNRI. In certain embodiments, the invention relates to the above-mentioned combination therapies of **CS1713** which further comprise CS1814.

DETD [0281] In certain embodiments, the combination therapy comprises CS1714 and a SSRI. In certain embodiments, the combination therapy comprises **CS1714** and a SNRI. In certain embodiments, the combination therapy comprises **CS1714**, a SSRI, and a SNRI. In certain embodiments, the invention relates to the above-mentioned combination therapies of **CS1714** which further comprise CS1814.

DETD [0282] In certain embodiments, the combination therapy comprises CS1814 and a SSRI. In certain embodiments, the combination therapy comprises **CS1814** and a SNRI. In certain embodiments, the combination therapy comprises **CS1814**, a SSRI, and a SNRI.

DETD [0328] Synthesis of **CS1628** and CS1648

DETD . . . ml-) and extracted with ethylacetate (2+200 mL), dried (MgSO4) and the solvent was reduced under reduced pressure to afford crude **CS1628**, which was purified by column chromatography on silica gel using heptane/ethyl actetate 5:1 as an eluent to afford CS1628 (2.2 g, 36%) as an off white solid.

DETD [0331] Synthesis of **CS1649** and **CS1658**

DETD . . . mL three neck round bottom flask, equipped with a stir bar, a thermometer and a gas adapter was charged with **CS1628** (2.2 g, 7.27 mmol) and dichloromethane (200 mL), cooled to -35° C. followed by the addition of a solution borontribromide. . . mL), extracted with ethyl acetate (2+200 mL), dried (MgSO4) and the solvent was reduced under reduced pressure to afford crude CS1649, which was purified by column chromatography on silica gel using heptane/ethyl actetate 2:1 as an eluent to afford CS1649 (1.39 g, 66.5 %) as an off white solid.

DETD [0333] In a similar fashion the desired enantiomer **CS1658** was

synthesized.
DETD [0334] Synthesis of **CS1665** and **CS1710**
DETD [0335] A 200 mL hydrogenation bottle was charged with **CS1649** (1.1 g, 3.81 mmol), methanol (50 ml-) and catalytic amounts of Pd/C. The reaction was subjected to 1 bar of. . . to afford crude CS1655, which was purified by column chromataograph on silica gel using dichloromethane/methanol/triethylamine 10:0.5:0.25 as eluent to afford CS1665 (0.80 g, 80%) as an of white solid.
DETD [0336] In a similar fashion the desired enantiomer **CS1710** was synthesized.

Analytical Data for **CS1665**

Appearance: Off white solid
.sup.1H NMR (MeOd-4):
.sup.13C{.sup.1H} NMR (apt):
(MeOd-4)
Optical Rotation [a].sup.20.sub.D -89
(c 0.5, Methanol):
IR (KBr, Neat, Solvent): N/A
HPLC: Purity: 97%. . .
DETD [0337]

Analytical Data for **CS1710**

Appearance: Off white solid
.sup.1H NMR (MeOd-4):
.sup.13C{.sup.1H}-NMR (apt)
(MeOd-4):
Optical Rotation [a].sup.20.sub.D +86.2
(c 0.5, Methanol):
IR (KBr, Neat, Solvent): N/A
HPLC: Purity: 98% @. . .
DETD [0338] Synthesis of **CS1713** and **CS1714**
DETD [0339] A 10 mL round bottom flask was charged with **CS1665** (0.51 g, 1.71 mmol) and hydrochloric acid in dioxane (5 mol/L, 10 mL). The mixture was stirred for 1 hour at room temperature, followed by removal of the solvent under reduced pressure to afford **CS1713** (0.43 g, 84%) as an off white solid.
DETD [0340] In a similar fashion the desired enantiomer **CS1714** was synthesized.

Analytical Data for **CS1713**

Appearance: Off white solid
.sup.1H NMR (MeOd-4):
.sup.13C{.sup.1H}-NMR (apt)
(MeOd-4):
Optical Rotation [a].sup.20.sub.D +80
(c 0.1, Methanol):
IR (KBr, Neat, Solvent): N/A
HPLC: Purity: 97% @. . .
DETD [0341]

Analytical Data for **CS1714**

Appearance: Off white solid
.sup.1H NMR (MeOd-4):
.sup.13C{.sup.1H}-NMR
(apt) (MeOd-4):
Optical Rotation [a].sup.20.sub.D -74
(c 0.1, Methanol):
IR (KBr, Neat, Solvent): N/A
HPLC: Purity: 96% @. . .

DETD [0342] Preparation of **CS1814**

DETD [0343] A 10 mL flask equipped with a magnetic stir bar was charged with CS1665/2 (120 mg, 0.46 mmol), **CS1710**/1 (120 mg, 0.46 mmol) and hydochloric acid in dioxan (5 mol/L, 5 ml). The suspension was stirred for 1 hour,. . . in dioxan (5 mol/L, 1 mL). The suspension was stirred for another hour and reduced under reduced pressure to afford **CS1814** (240 mg, quant) as an off white solid. The solid was dissolved in methanol (10 mL, homogenous solution), transferred to. . . combined with the above solution (total volume of approximately 15 mL, homogenous solution) and reduced under reduced pressure to afford CS1814 (240 mg, quant) as an off white solid. The solid was dried under high vacuum. 50 mg of this material. . . later transferred back to the 20 mL flask (homogenous solution) and the solvent removed under reduced pressure.

Analytical Data for **CS1814**

Appearance: Off white solid
.sup.1H NMR (MeOd-4):
.sup.13C{.sup.1H}-NMR (apt)
(MeOd-4):
Optical Rotation [a].sup.20.sub.D 0 racemic
(c 0.5, Methanol):
IR (KBr, Neat, Solvent): N/A
HPLC: Purity: 97%. . .

DETD [0344] Biological Testing of **CS1814** and Reference Compounds

DETD [0345] The results from the biological testing of **CS1814** and various reference compounds are presented in FIGS. 32-40 and 59. The data in FIG. 59 indicate that **CS1814** has an IC.sub.50=0.22 μM for inhibition of norepinephrine transporter and an IC.sub.50 value of 12.7 nM for inhibition of serotonin transporter. The binding constants for **CS1814** are Ki=0.218 μM for norepinephrine transporter and Ki=6.73 nM for serotonin transporter.

DETD [0448] Biological Testing of **CS1814**, **CS1713**, and CS1714

DETD [0449] The results from the biological testing of **CS1814**, CS1713, **CS1714**, and various reference compounds are presented in FIGS. 41-58 and 60-62. The methods employed have been adapted from the scientific. . .

DETD [0452] **CS1713** (Vial #2), **CS1714** (Vial #3), and CS1814 (Vial #1) were evaluated for inhibition of cellular Serotonin and Norepinephrine Uptake. In addition, **CS1713** (Vial #2) and **CS1714** (Vial #3) were evaluated in various radioligand binding assays, and for inhibition of CYP450 3A4 at initial concentrations of 10. . .

DETD [0453] As depicted in FIG. 61, **CS1814** (Vial #1) is approximately equipotent in inhibiting serotonin and norepinephrine uptake (IC.sub.50=28.6 nM for norepinephrine, IC.sub.50=21.7 nM for serotonin). Interestingly, **CS1713** (Vial #2) is a more potent inhibitor of norepinephrine uptake than serotonin uptake (IC.sub.50=10.3 nM for norepinephrine, IC.sub.50=22 nM for serotonin). In contrast, CS1714 (Vial #3) is a more potent inhibitor of serotonin uptake

compared to norepinephrin uptake (IC.sub.50=88.5 nM for norepinephrine, IC.sub.50=40.3 nM for serotonin). The fact that **CS1713** (Vial #2) is a more potent inhibitor of norepinephrine uptake would render it a superior therapeutic agent for treating diseases linked to norepinephrine uptake. In addition, the **CS1714** (Vial #3) would useful for treating conditions requiring selective inhibition of serotonin uptake.

DETD [0454] Importantly, no cytotoxicity was observed for **CS1713** (Vial #2), **CS1714** (Vial #3), or **CS1814** (Vial #1) at 10 μM. In addition, **CS1814** (Vial #1) is a selective inhibitor of norepinephrine and serotonin transporters. The fact that CS1814 generally does not bind well to other receptors, as depicted in FIGS. 32 and 33, substantially reduces the risk of negative side effects associated with administering the compound to a patient. Therefore, it is likely that **CS1713** and **CS1714** will not have detrimental side effects.

CLM What is claimed is:

39. The composition of any one of claims 35-37, wherein said compound of claim 1 or 2 is **CS1713.**

40. The composition of any one of claims 35-37, wherein said compound of claim 1 or 2 is **CS1714.**

41. The composition of any one of claims 35-40, wherein said composition further comprises **CS1814.**

42. A composition comprising a selective serotonin reuptake inhibitor and **CS1814.**

43. A composition comprising a selective norepinephrine reuptake inhibitor and **CS1814.**

44. A composition comprising a selective serotonin reuptake inhibitor, a selective norepinephrine reuptake inhibitor, and **CS1814.**

L25 ANSWER 4 OF 9 USPATFULL on STN
AN 2004:172662 USPATFULL
TI Modified release compositions of milnacipran
IN Hirsh, Jane, Wellesley, MA, UNITED STATES
Rariy, Roman V., Allston, MA, UNITED STATES
Chungi, Shubha, Sharon, MA, UNITED STATES
Heffernan, Michael, Hingham, MA, UNITED STATES
Rao, Srinivas G., San Diego, CA, UNITED STATES
PA Collegium Pharmaceutical, Inc. (U.S. corporation)
Cypress Bioscience, Inc. (U.S. corporation)
PI US 2004132826 A1 20040708
AI US 2003-690947 A1 20031022 (10)
PRAI US 2002-421640P 20021025 (60)
US 2002-431626P 20021205 (60)
US 2002-431627P 20021205 (60)
US 2002-431906P 20021209 (60)
US 2002-431861P 20021209 (60)
US 2003-443618P 20030129 (60)
US 2003-459061P 20030328 (60)
US 2003-458994P 20030328 (60)
US 2003-458995P 20030328 (60)
DT Utility
FS APPLICATION
LREP PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
CLMN Number of Claims: 24
ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)
LN.CNT 1390
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A once-a-day oral milnacipran modified release formulation has been developed. The formulation comprises an extended release dosage unit (optionally containing the immediate release portion) coated with delayed release coating. The milnacipran composition, when administered orally, first passes through the stomach releasing from zero to less than 10% of the total milnacipran dose and then enters the intestines where drug is released slowly over an extended period of time. The release profile is characterized by a 0.05-4 hours lag time period during which less than 10% of the total milnacipran dose is released followed by a slow or extended release of the remaining drug over a defined period of time. The composition provides in vivo drug plasma levels characterized by T.sub.max at 4-10 hours and an approximately linear drop-off thereafter and C.sub.max below 3000 ng/ml, preferably below 2000 ng/ml, and most preferably below 1000 ng/ml. The composition allows milnacipran to be delivered over approximately 24 hours, when administered to a patient in need, resulting in diminished incidence or decreased intensity of common milnacipran side effects such as sleep disturbance, nausea, vomiting, headache, tremulousness, anxiety, panic attacks, palpitations, urinary retention, orthostatic hypotension, diaphoresis, chest pain, rash, weight gain, back pain, constipation, vertigo, increased sweating, agitation, hot flushes, tremors, fatigue, somnolence, dyspepsia, dysoria, nervousness, dry mouth, abdominal pain, irritability, and insomnia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
14. The milnacipran formulation according to claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (**F2782**) or pharmaceutically acceptable salts thereof.

L25 ANSWER 5 OF 9 USPATFULL on STN
AN 2004:159300 USPATFULL
TI Modified release compositions of milnacipran
IN Hirsh, Jane, Wellesley, MA, UNITED STATES
Rariy, Roman V., Allston, MA, UNITED STATES
Chungi, Shubha, Sharon, MA, UNITED STATES
Heffernan, Michael, Hingham, MA, UNITED STATES
PA Collegium Pharmaceutical, Inc. (U.S. corporation)
PI US 2004122104 A1 20040624
AI US 2003-691936 A1 20031023 (10)
PRAI US 2002-421640P 20021025 (60)
US 2002-431626P 20021205 (60)
US 2002-431627P 20021205 (60)
US 2002-431906P 20021209 (60)
US 2002-431861P 20021209 (60)
US 2003-443618P 20030129 (60)
US 2003-459061P 20030328 (60)
US 2003-458994P 20030328 (60)
US 2003-458995P 20030328 (60)
DT Utility
FS APPLICATION
LREP PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 1388
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A once-a-day oral milnacipran modified release formulation has been developed. The formulation comprises an extended release dosage unit (optionally containing the immediate release portion) coated with delayed release coating. The milnacipran composition, when administered orally, first passes through the stomach releasing from zero to less than 10% of the total milnacipran dose and then enters the intestines where drug is released slowly over an extended period of time. The release profile is characterized by a 0.05-4 hours lag time period during which less than 10% of the total milnacipran dose is released followed by a slow or extended release of the remaining drug over a defined period of time. The composition provides in vivo drug plasma levels characterized by T.sub.max at 4-10 hours and an approximately linear drop-off thereafter and C.sub.max below 3000 ng/ml, preferably below 2000 ng/ml, and most preferably below 1000 ng/ml. The composition allows milnacipran to be delivered over approximately 24 hours, when administered to a patient in need, resulting in diminished incidence or decreased intensity of common milnacipran side effects such as sleep disturbance, nausea, vomiting, headache, tremulousness, anxiety, panic attacks, palpitations, urinary retention, orthostatic hypotension, diaphoresis, chest pain, rash, weight gain, back pain, constipation, vertigo, increased sweating, agitation, hot flushes, tremors, fatigue, somnolence, dyspepsia, dysoria, nervousness, dry mouth, abdominal pain, irritability, and insomnia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
. . . milnacipran formulation according to claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (**F2782**) or pharmaceutically acceptable salts thereof.

L25 ANSWER 6 OF 9 USPATFULL on STN
AN 2004:158213 USPATFULL
TI Pulsatile release compositions of milnacipran
IN Hirsh, Jane, Wellesley, MA, UNITED STATES
Rariy, Roman V., Allston, MA, UNITED STATES
Heffernan, Michael, Hingham, MA, UNITED STATES
PA Collegium Pharmaceutical, Inc. (U.S. corporation)
PI US 2004121010 A1 20040624
AI US 2003-690872 A1 20031022 (10)
PRAI US 2002-421640P 20021025 (60)
US 2002-431626P 20021205 (60)
US 2002-431627P 20021205 (60)
US 2002-431906P 20021209 (60)
US 2002-431861P 20021209 (60)
US 2003-443618P 20030129 (60)
US 2003-459061P 20030328 (60)
US 2003-458994P 20030328 (60)
US 2003-458995P 20030328 (60)
DT Utility
FS APPLICATION
LREP PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1610
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A once-a-day oral milnacipran pulsatile release composition has been developed that releases the drug in spaced apart "pulses". The dosage forms are comprised of first, second and optional third dosage units, with each dosage unit having a different drug release profile. This

dosage form provides in vivo drug plasma levels characterized by C.sub.max below 3000 ng/ml, preferably below 2000 ng/ml, and most preferably below 1000 ng/ml. These levels help to avoid stimulation of the cholinergic effects on the CNS. The composition allows milnacipran to be delivered over approximately 24 hours, when administered to a patient in need, resulting in diminished incidence or decreased intensity of common milnacipran side effects such as sleep disturbance, nausea, vomiting, headache, tremulousness, anxiety, panic attacks, palpitations, urinary retention, orthostatic hypotension, diaphoresis, chest pain, rash, weight gain, back pain, constipation, vertigo, increased sweating, agitation, hot flushes, tremors, fatigue, somnolence, dyspepsia, dysoria, nervousness, dry mouth, abdominal pain, irritability, and insomnia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
. . . milnacipran formulation according to claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (**F2782**) or pharmaceutically acceptable salts thereof.

L25 ANSWER 7 OF 9 USPATFULL on STN
AN 2004:133881 USPATFULL
TI Compounds for the treatment of inflammatory disorders
IN Zhu, Zhoaning, Plainsboro, NJ, UNITED STATES
Mazzola, Robert, Clinton, NJ, UNITED STATES
Guo, Zhuyan, Scotch Plains, NJ, UNITED STATES
Lavey, Brian J., Chatham, NJ, UNITED STATES
Sinning, Lisa, New Providence, NJ, UNITED STATES
Kozlowski, Joseph, Princeton, NJ, UNITED STATES
McKittrick, Brian, New Vernon, NJ, UNITED STATES
Shih, Neng-Yang, North Caldwell, NJ, UNITED STATES
PI US 2004102418 A1 20040527
AI US 2003-716890 A1 20031119 (10)
RLI Division of Ser. No. US 2002-323511, filed on 19 Dec 2002, PENDING
PRAI US 2001-342332P 20011220 (60)
DT Utility
FS APPLICATION
LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 65
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3496
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to compounds of the Formula (I): ##STR1##

or a pharmaceutically acceptable salt, solvate or isomer thereof, which can be useful for the treatment of diseases or conditions mediated by MMPs, TNF-α or combinations thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 556105-11-4P 556105-12-5P 556105-13-6P 556105-14-7P 556105-15-8P
556105-16-9P 556105-17-0P 556105-19-2P 556105-20-5P 556105-22-7P
556105-23-8P 556105-24-9P 556105-26-1P 556105-27-2P 556105-28-3P
556105-29-4P 556105-30-7P 556105-32-9P 556105-33-0P 556105-34-1P
556105-35-2P 556105-36-3P 556105-37-4P 556105-38-5P 556105-40-9P
556105-41-0P 556105-42-1P 556105-43-2P 556105-44-3P 556105-45-4P
556105-46-5P 556105-47-6P 556105-48-7P 556105-49-8P 556105-50-1P
556105-51-2P 556105-52-3P 556105-53-4P **556105-54-5P**
556105-55-6P 556105-56-7P 556105-57-8P 556105-58-9P 556105-59-0P
556105-60-3P 556105-61-4P 556105-62-5P 556105-63-6P 556105-64-7P

556105-65-8P 556105-66-9P 556105-67-0P 556105-68-1P 556105-69-2P
556105-70-5P 556105-71-6P 556105-72-7P 556105-73-8P 556105-74-9P
556105-76-1P 556105-78-3P 556105-80-7P 556105-81-8P 556105-82-9P
556105-83-0P 556105-84-1P 556105-85-2P 556105-86-3P 556105-87-4P
556105-88-5P 556105-89-6P 556105-90-9P 556105-91-0P 556105-92-1P
556105-93-2P 556105-94-3P 556105-95-4P 556105-96-5P 556105-97-6P
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556106-03-7P 556106-04-8P 556106-05-9P 556106-06-0P 556106-07-1P
556106-08-2P 556106-09-3P 556106-10-6P 556106-11-7P 556106-12-8P
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556106-23-1P 556106-24-2P 556106-25-3P 556106-26-4P 556106-27-5P
556106-28-6P 556106-29-7P 556106-30-0P 556106-31-1P 556106-32-2P
556106-33-3P 556106-34-4P 556106-35-5P 556106-36-6P 556106-37-7P
556106-38-8P 556106-39-9P 556106-40-2P 556106-41-3P 556106-42-4P
556106-43-5P 556106-44-6P 556106-45-7P 556106-46-8P 556106-47-9P
556106-48-0P 556106-49-1P 556106-50-4P 556106-51-5P 556106-52-6P
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556106-58-2P 556106-59-3P 556106-60-6P 556106-61-7P 556106-62-8P
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556106-78-6P 556106-79-7P 556106-80-0P 556106-81-1P 556106-82-2P
556106-83-3P 556106-84-4P 556106-85-5P 556106-86-6P 556106-87-7P
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556106-93-5P 556106-94-6P 556106-95-7P 556106-96-8P 556106-97-9P
556106-98-0P 556106-99-1P 556107-01-8P 556107-02-9P 556107-03-0P
556107-04-1P 556107-05-2P 556107-06-3P 556107-07-4P 556107-08-5P
556107-09-6P 556107-10-9P 556107-11-0P 556107-12-1P 556107-13-2P
556107-14-3P 556107-15-4P 556107-16-5P 556107-17-6P 556107-18-7P
556107-19-8P 556107-20-1P 556107-21-2P 556107-22-3P 556107-23-4P
556107-24-5P 556107-25-6P 556107-26-7P 556107-27-8P 556107-28-9P
556107-29-0P 556107-30-3P 556107-31-4P 556107-32-5P 556107-33-6P
556107-34-7P 556107-35-8P 556107-36-9P 556107-37-0P 556107-38-1P
556107-39-2P 556107-40-5P 556107-41-6P 556107-42-7P 556107-43-8P
556107-45-0P 556107-46-1P 556107-47-2P 556107-48-3P 556107-49-4P
556107-51-8P 556107-52-9P 556107-54-1P 556107-56-3P 556107-57-4P
556107-59-6P

(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556107-60-9P 556107-62-1P 556107-63-2P 556107-65-4P 556107-66-5P
556107-68-7P 556107-69-8P 556107-71-2P 556107-73-4P 556107-75-6P
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556107-88-1P 556107-90-5P 556107-92-7P 556107-94-9P 556107-95-0P
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556108-07-7P 556108-09-9P 556108-11-3P 556108-13-5P 556108-15-7P
556108-17-9P 556108-18-0P 556108-20-4P 556108-22-6P 556108-24-8P
556108-26-0P 556108-28-2P 556108-30-6P 556108-32-8P 556108-34-0P
556108-36-2P 556108-38-4P 556108-40-8P 556108-42-0P 556108-43-1P
556108-45-3P 556108-47-5P 556108-49-7P 556108-51-1P 556108-53-3P
556108-55-5P 556108-57-7P 556108-59-9P 556108-61-3P 556108-63-5P
556108-65-7P 556108-67-9P 556108-69-1P 556108-71-5P 556108-73-7P
556108-75-9P 556108-77-1P 556108-79-3P 556108-81-7P 556108-83-9P
556108-84-0P 556108-86-2P 556108-88-4P 556108-90-8P 556108-92-0P
556108-93-1P 556108-95-3P 556108-97-5P 556108-99-7P 556109-02-5P
556109-05-8P 556109-07-0P 556109-09-2P 556109-11-6P
556109-14-9P 556109-16-1P 556109-18-3P 556109-20-7P 556109-22-9P
556109-24-1P 556109-26-3P 556109-28-5P 556109-30-9P 556109-32-1P
556109-34-3P 556109-36-5P 556109-38-7P 556109-40-1P 556109-42-3P
556109-44-5P 556109-46-7P 556109-48-9P 556109-50-3P 556109-53-6P
556109-55-8P 556109-59-2P 556109-61-6P 556109-63-8P 556109-65-0P
556109-67-2P 556109-69-4P 556109-71-8P 556109-72-9P 556109-73-0P

556109-74-1P 556109-75-2P
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)
IT **556105-54-5P 556109-05-8P**
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

L25 ANSWER 8 OF 9 USPATFULL on STN
AN 2004:51510 USPATFULL
TI Compounds for the treatment of inflammatory disorders
IN Zhu, Zhaoning, Plainsboro, NJ, UNITED STATES
Mazzola, Robert, Clinton, NJ, UNITED STATES
Guo, Zhuyan, Scotch Plains, NJ, UNITED STATES
Lavey, Brian J., Chatham, NJ, UNITED STATES
Sinning, Lisa, New Providence, NJ, UNITED STATES
Kozlowski, Joseph, Princeton, NJ, UNITED STATES
McKittrick, Brian, New Vernon, NJ, UNITED STATES
Shih, Neng-Yang, North Caldwell, NJ, UNITED STATES
PA Schering Corporation (U.S. corporation)
PI US 2004038941 A1 20040226
AI US 2002-323511 A1 20021219 (10)
PRAI US 2001-342332P 20011220 (60)
DT Utility
FS APPLICATION
LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 65
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3458
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to compounds of the Formula (I): ##STR1##

or a pharmaceutically acceptable salt, solvate or isomer thereof, which can be useful for the treatment of diseases or conditions mediated by MMPs, TNF-α or combinations thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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556107-59-6P
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT 556107-60-9P 556107-62-1P 556107-63-2P 556107-65-4P 556107-66-5P
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556109-67-2P 556109-69-4P 556109-71-8P 556109-72-9P 556109-73-0P
556109-74-1P 556109-75-2P
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

IT **556105-54-5P 556109-05-8P**
(preparation of hydroxamic or carboxylic acid functionalized cycloalkanes as inhibitors of tumor necrosis factor alpha and/or matrix metalloproteinases)

L25 ANSWER 9 OF 9 USPATFULL on STN
AN 84:59677 USPATFULL
TI 1-Aryl 2-aminomethyl cyclopropane carboxyamide (Z) derivatives and their use as useful drugs in the treatment of disturbances of the central

nervous system
IN Mouzin, Gilbert, Castres, France
Cousse, Henri, Castres, France
Bonnaud, Bernard, Castres, France
Morre, Michel, Toulouse, France
Stenger, Antoine, Castres, France
PA Pierre Fabre S.A., Castres, France (non-U.S. corporation)
PI US 4478836 19841023
AI US 1982-390810 19820622 (6)
PRAI FR 1981-12312 19810623
DT Utility
FS Granted
EXNAM Primary Examiner: Shippen, Michael L.
LREP Hueschen, Gordon W.
CLMN Number of Claims: 16
ECL Exemplary Claim: 1,12
DRWN No Drawings
LN.CNT 520
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention concerns new derivatives of 1-aryl 2-aminomethyl cyclopropane carboxamides (Z) of general formula I: ##STR1## in which: R represents a hydrogen or halogen atom, a lower alkyl group, a lower alkoxy group, or a hydroxy. nitro or amino group;

n represents the value 1 or 2;

R.sub.1 and R.sub.2 represent a hydrogen atom, a lower alkyl group, an aryl or lower alkaryl group, possibly substituted, preferably in para position, by a halogen atom, preferably a chlorine atom;

R.sub.1 and R.sub.2 may also form a heterocycle having 5 or 6 members with the adjacent nitrogen atom;

R.sub.3 and R.sub.4 represent a hydrogen atom or a lower alkyl group;

R.sub.3 and R.sub.4 may also form with the adjacent nitrogen atom a heterocycle having 5 or 6 members, possibly containing an additional heteroatom selected from among nitrogen and oxygen,

as well as their salts with therapeutically acceptable inorganic or organic acids, and their pharmaceutical compositions and use in the treatment of central nervous system disturbances, e.g., depression.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 86181-09-1P 86181-11-5P 86181-12-6P 86181-13-7P 86181-14-8P
86181-15-9P 86181-16-0P **86181-17-1P** **86181-18-2P**
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(preparation of)
IT **86181-17-1P** **86181-18-2P** **86181-19-3P**
86181-21-7P
(preparation of)

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L2 497 S COLLEGIUM?/PA,CS
E RARIY R/AU

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L3            16 S E4-E6
                 E HEFFERNAN M/AU
L4            67 S E3-E6,E11-E16,E19
                 E BUCHWALD S/AU
L5           327 S E3,E4,E6-E9
                 E SWAGER T/AU
L6           340 S E3-E9

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L8             3 S L7
L9            25 S L7 FUL
                 SAV L9 KUMAR691/A
                 E CS1713/CN
                 E CS 1713/CN
L10            3 S E3,E4,E10
L11           22 S L9 NOT L10

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L18            3 S L17 AND L1-L6
L19            2 S F2782 OR CS1628 OR CS1649 OR CS1665 OR CS1710 OR CS1658
L20            3 S F 2782 OR CS()(1628 OR 1649 OR 1665 OR 1710 OR 1658)
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L25            9 S L23,L24

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     FILE 'USPATFULL' ENTERED AT 08:12:57 ON 01 DEC 2004

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